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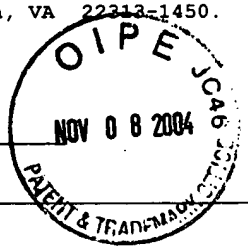
Date: November 4, 2004



Bernard Lau
(Print Name)

(Signature)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1625

David William Banner, et al.

Serial No.: 10/720,790

Filed: November 21, 2003

For: **NOVEL MANDELIC ACID DERIVATIVES**

TRANSMITTAL OF CERTIFIED COPY

November 4, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	02026365.3	November 25, 2002

Respectfully submitted,

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BL/bah
Enclosure

Europäisches Patentamt | European Patent Office | Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02026365.3

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

CERTIFIED COPY OF PRIORITY DOCUMENT

Europäisches Patentamt | European Patent Office | Office européen des brevets

Anmeldung Nr:
Application no.: 02026365.3
Demande no:

Anmeldetag:
Date of filing: 25.11.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

F. HOFFMANN-LA ROCHE AG

4070 Basel
SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Novel mandelic acid derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D213/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

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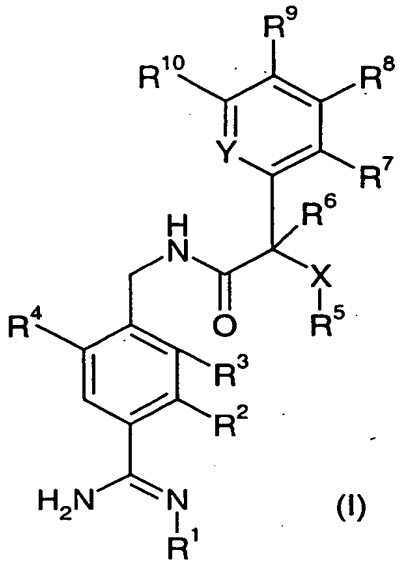
Case 21500

Novel mandelic acid derivatives

The invention is concerned with novel mandelic acid derivatives of the formula (I)



(I)

wherein

R^1 is hydrogen, OH, NH_2, lower-alkoxy-carbonyl, aryl-lower-alkoxy-carbonyl, aryloxy-carbonyl, lower-alkyl-carbonyl, aryl-carbonyl, or lower-alkoxy-carbonyl which is substituted with halogen;

R^2, R^3 and R^4 independently from each other are selected from the group consisting of hydrogen, halogen, hydroxy, and lower-alkoxy, which lower-alkoxy can optionally be substituted with hydroxy, carboxy or carbamoyl;

R^5 is lower-alkyl or cycloalkyl, or, if X is O or NR^{12}, R^5 can also be hydrogen;

R^6 is hydrogen, lower-alkyl, or fluoro-lower-alkyl;

Y is N or C-R^{11};

R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, hydroxy, halogen, amino, lower-alkyl-amino, di-lower-alkyl-amino, lower-alkyl-carbonyl-amino, NO_2, fluoro-lower-alkyl, lower-alkoxy, hydroxy-lower-alkoxy, fluoro-lower-alkoxy, lower-alkinyl, hydroxy-lower-alkinyl, aryl, aryl-lower-alkoxy, aryloxy, aryloxy-lower-alkoxy, heterocyclyl, heterocyclyloxy, lower-alkoxy-carbonyl-lower-alkoxy, carbamoyl-lower-alkoxy, carboxy-lower-alkoxy, cycloalkyloxy, heteroaryl, amino-lower-alkoxy, lower-alkyl-amino-lower-alkoxy, and di-lower-alkyl-amino-lower-alkoxy,

or

R^8 and R^9 or R^8 and R^7 are bound to each other to form a ring together with the carbon atoms to which they are attached and R^8 and R^9 together or R^8 and R^7 together are -O-CH_2-O-, -O-CH_2-CO-NH-, -O-CH_2-CH_2-CH_2-, or -CH=CH-CH=CH-, which can optionally be substituted with lower-alkyl or lower-alkoxy, and R^{10}, R^{11} and R^7 or R^9 respectively are as definde above;

X is O, S, NR^{12}, or SO_2;

R^{12} is hydrogen, lower-alkyl, or lower-alkyl-carbonyl;

and pharmaceutically acceptable salts thereof.

Further, the invention is concerned with a process for the manufacture of the above compounds, pharmaceutical preparations which contain such compounds as well as the use of these compounds for the production of pharmaceutical preparations.

The compounds of formula (I) are active compounds and inhibit the formation of coagulation factors Xa, IXa and thrombin induced by factor VIIa and tissue factor or are derivatives which are converted under physiological conditions to such active compounds. These compounds consequently influence both platelet aggregation which is induced by these factors and plasmatic blood coagulation. They therefore inhibit the formation of thrombi and can be used for the treatment and/or prevention of diseases, such as arterial and venous thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation and arteriosclerosis. Furthermore, these compounds have an effect on tumour cells and prevent metastases. They can therefore also be used as antitumour agents.

Inhibitors of factor VIIa had previously been suggested for the inhibition of the formation of thrombi and for the treatment of related diseases (WO 00/35858). However,

there is still a need for novel factor VIIa inhibitors which exhibit improved pharmacological properties.

The present invention provides the novel compounds of formula (I) which are factor VIIa inhibitors. The compounds of the present invention exhibit improved pharmacological properties compared to the known compounds.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms. Lower-alkyl groups as described below also are preferred alkyl groups.

The term "lower-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like.

The term "fluoro-lower-alkyl" refers to lower-alkyl groups which are mono- or multiply substituted with fluorine. Examples of fluoro-lower-alkyl groups are e.g. CFH_2, CF_2H, CF_3, CF_3CH_2, $(CF_3)_2CH$ and CF_2H-CF_2

The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atoms, preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "cycloalkyloxy" refers to the group cycloalkyl-O-.

The term "alkoxy" refers to the group R'-O-, wherein R' is an alkyl. The term "lower-alkoxy" refers to the group R'-O-, wherein R' is a lower-alkyl.

The term "fluoro-lower-alkoxy" refers to the group R"-O-, wherein R" is fluoro-lower-alkyl. Examples of fluoro-lower-alkoxy groups are e.g. CFH_2-O, CF_2H-O, CF_3-O, CF_3CH_2-O, $(CF_3)_2CH$-O and CF_2H-CF_2-O,

The term "alkinyl", alone or in combination with other groups, stands for a straight-chain or branched hydrocarbon residue comprising a tripple bond and up to 20, preferably up to 16 carbon atoms. The term "lower-alkinyl" refers to a straight-chain or branched hydrocarbon residue comprising a tripple bond and 2 to 7, preferably 2 to 4 carbon atoms, such as e.g. 2-propinyl.

The term "aryl" relates to the phenyl or naphthyl group, preferably the phenyl group, which can optionally be substituted by 1 to 5 , preferably 1 to 3, substituents independently selected from the group consisting of lower-alkyl, lower-alkenyl, lower-alkinyl, dioxo-lower-alkylene (forming e.g. a benzodioxyl group), halogen, hydroxy, CN, CF_3, NH_2, N(H, lower-alkyl), N(lower-alkyl)$_2$, aminocarbonyl, carboxy, NO_2, lower-alkoxy, thio-lower-alkoxy, lower-alkylcarbonyl, lower-alkylcarbonyloxy, lower-alkoxycarbonyl. Preferred substituents are halogen, CF_3, CN, NH_2, N(H, lower-alkyl), N(lower-alkyl)$_2$, lower-alkyl and/or lower-alkoxy.

The term "aryloxy" refers to the group aryl-O-.

The term "heterocyclyl" as used herein denotes non-aromatic monocyclic heterocycles with 5 or 6 ring members, which comprise 1, 2 or 3 hetero atoms selected from nitrogen, oxygen and sulfur. Examples of suitable heterocycles are pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, morpholinyl, pyranyl, tetrahydropyranyl, 4,5-dihydro-oxazolyl, 4,5-dihydro-thiazolyl. A heterocyclyl group may have a substitution pattern as described earlier in connection with the term "aryl". Lower-alkyl substituents are preferred.

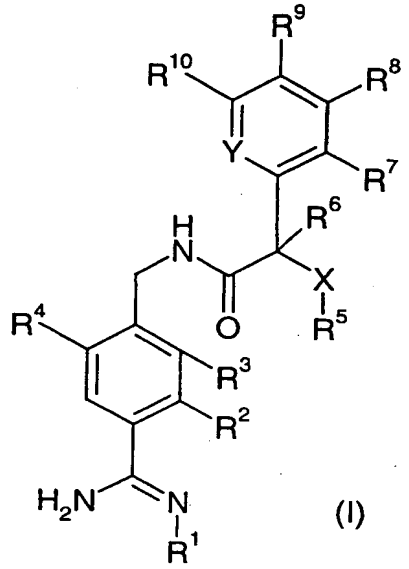
The term "heterocyclyloxy" refers to the group heterocyclyl-O-.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur, such as furyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, oxazolyl, imidazolyl, pyrrolyl, or tetrazolyl. A heteroaryl group may have a substitution pattern as described earlier in connection with the term "aryl".

Compounds of formula (I) can form pharmaceutically acceptable acid addition salts. Examples of such pharmaceutically acceptable salts are salts of compounds of formula (I) with physiologically compatible mineral acids, such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The term "pharmaceutically acceptable salts" refers to such salts. Compounds of formula (I) in which a COOH group is

present can further form salts with bases. Examples of such salts are alkaline, earth-alkaline and ammonium salts such as e.g. Na-, K-, Ca- and Trimethylammoniumsalt. The term "pharmaceutically acceptable salts" also refers to such salts. Acid addition salts as described above are preferred.

In detail, the present invention relates to compounds of formula (I)



(I)

wherein

R^1 is hydrogen, OH, NH_2, lower-alkoxy-carbonyl, aryl-lower-alkoxy-carbonyl, aryloxy-carbonyl, lower-alkyl-carbonyl, aryl-carbonyl, or lower-alkoxy-carbonyl which is substituted with halogen;

R^2, R^3 and R^4 independently from each other are selected from the group consisting of hydrogen, halogen, hydroxy, and lower-alkoxy, which lower-alkoxy can optionally be substituted with hydroxy, carboxy or carbamoyl;

R^5 is lower-alkyl or cycloalkyl, or, if X is O or NR^{12}, R^5 can also be hydrogen;

R^6 is hydrogen, lower-alkyl, or fluoro-lower-alkyl;

Y is N or C-R^{11};

R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, hydroxy, halogen, amino, lower-alkyl-amino, di-lower-alkyl-amino, lower-alkyl-carbonyl-amino, NO_2, fluoro-lower-alkyl, lower-alkoxy, hydroxy-lower-alkoxy, fluoro-lower-alkoxy, lower-alkinyl, hydroxy-lower-alkinyl, aryl, aryl-lower-alkoxy, aryloxy, aryloxy-lower-alkoxy, heterocyclyl, heterocyclyloxy, lower-alkoxy-carbonyl-lower-alkoxy, carbamoyl-lower-alkoxy, carboxy-lower-alkoxy, cycloalkyloxy, heteroaryl, amino-lower-alkoxy, lower-alkyl-amino-lower-alkoxy, and di-lower-alkyl-amino-lower-alkoxy,

or

R^8 and R^9 or R^8 and R^7 are bound to each other to form a ring together with the carbon atoms to which they are attached and R^8 and R^9 together or R^8 and R^7 together are -O-CH_2-O-, -O-CH_2-CO-NH-, -O-CH_2-CH_2-CH_2-, or -CH=CH-CH=CH-, which can optionally be substituted with lower-alkyl or lower-alkoxy, and R^{10}, R^{11} and R^7 or R^9 respectively are as definde above;

X is O, S, NR^{12}, or SO_2;

R^{12} is hydrogen, lower-alkyl, or lower-alkyl-carbonyl;

and pharmaceutically acceptable salts thereof.

The compounds of formula (I) have at least one asymmetric C atom and can therefore exist as an enantiomeric mixture, diastereomeric mixture or as optically pure compounds. Compounds of formula (I) can exist in tautomeric forms and the invention encompasses all such tautomeric forms.

Compounds of formula (I) are individually preferred and physiologically acceptable salts thereof are individually preferred, with the compounds of formula (I) being particularly preferred.

Preferred compounds of formula (I) are those, wherein R^1 is hydrogen, OH, NH_2, or lower-alkoxy-carbonyl, preferably those, wherein R^1 is hydrogen, OH, or lower-alkoxy-carbonyl, more preferably those wherein R^1 is hydrogen, OH, or ethoxycarbonyl, and most preferably those wherein R^1 is hydrogen. Another preferred embodiment of the present invention relates to compounds as described above, wherein R^2, R^3 and R^4 independently from each other are hydrogen or halogen, with those compounds wherein R^2, R^3 and R^4 are hydrogen being most preferred.

In a further preferred embodiment the invention relates to compounds as described above in which X is O. Compounds in which R^5 is lower-alkyl, or, if X is O or NR^{12}, R^5 can also be hydrogen, are preferred. Compounds in which R^5 is lower-alkyl are also preferred, with those compounds wherein R^5 is methyl or ethyl being particularly preferred.

The invention embraces especially compounds in accordance with the above definitions in which R^6 is hydrogen, methyl or CF_3, preferably hydrogen.

In one preferred embodiment, R^8 and R^9 or R^8 and R^7 are not bound to each other to form a ring together with the carbon atoms to which they are attached. Moreover, the

invention relates especially to compounds as defined above wherein Y is C-R^{11} and R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, hydroxy, halogen, di-lower-alkyl-amino, lower-alkyl-carbonyl-amino, NO_2, fluoro-lower-alkyl, lower-alkoxy, hydroxy-lower-alkoxy, fluoro-lower-alkoxy, aryl, aryl-lower-alkoxy, aryloxy, aryloxy-lower-alkoxy, heterocyclyl, heterocyclyloxy, lower-alkoxy-carbonyl-lower-alkoxy, carbamoyl-lower-alkoxy, carboxy-lower-alkoxy, cycloalkyloxy, heteroaryl, and di-lower-alkyl-amino-lower-alkoxy. More preferably, Y is C-R^{11} and R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, halogen, lower-alkoxy, and pyridyl. Even more preferably, Y is C-R^{11} and R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, fluoro, bromo, methoxy, and pyridyl.

In another preferred embodiment of the present invention, Y is C-R^{11}, R^8 and R^9 or R^8 and R^7 are bound to each other to form a ring together with the carbon atoms to which they are attached and R^8 and R^9 together or R^8 and R^7 together are -O-CH_2-O-, -O-CH_2-CO-NH-, -O-CH_2-CH_2-CH_2-, or -CH=CH-CH=CH-, which can optionally be substituted with lower-alkyl or lower-alkoxy, and R^{10}, R^{11} and R^7 or R^9 respectively are hydrogen.

In particular, preferred compounds are the compounds of formula (I) described in the examples as individual compounds as well as pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I) are those selected from the group consisting of
(S)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-phenyl-acetamide hydrochloride,
(R)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-phenyl-acetamide hydrochloride,
(RS)-2-(4-Benzyloxy-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-(4-phenoxy-phenyl)-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-(3-phenoxy-phenyl)-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-ethoxy-2-phenyl-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-2-(3-Benzyloxy-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(3-hydroxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-(3-nitro-phenyl)-acetamide

hydrochloride,
(RS)-2-Biphenyl-4-yl-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
(RS)-2-Benzo[1,3]dioxol-5-yl-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
(RS)-2-Benzo[1,3]dioxol-5-yl-N-(4-carbamimidoyl-benzyl)-2-ethoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-[5-ethoxy-2-fluoro-3-(1-methyl-piperidin-4-yloxy)-phenyl]-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-[Amino-(4-{[2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetylamino]-methyl}-phenyl)-methylene]-carbamic acid ethyl ester,
(RS)-2-(2-Fluoro-4-methoxy-phenyl)-N-[4-(N-hydroxycarbamimidoyl)-benzyl]-2-methoxy-acetamide,
RS)-2-(2-Fluoro-4-methoxy-phenyl)-N-[4-(N-aminocarbamimidoyl)-benzyl]-2-methoxy-acetamide,
(RS)-{5-[(4-Carbamimidoyl-benzylcarbamoyl)-methoxy-methyl]-2-methoxy-phenoxy}-acetic acid methyl ester hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(3-carbamoylmethoxy-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-{5-[(4-Carbamimidoyl-benzylcarbamoyl)-ethoxy-methyl]-2-methoxy-phenoxy}-acetic acid ethyl ester hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(3-carbamoylmethoxy-4-methoxy-phenyl)-2-ethoxy-acetamide hydrochloride,
(RS)-{5-[(4-Carbamimidoyl-benzylcarbamoyl)-ethoxy-methyl]-2-methoxy-phenoxy}-acetic acid,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-ethoxy-2-(4-ethoxy-phenyl)-acetamid hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-[4-(1-methyl-piperidin-4-yloxy)-phenyl]-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4,5-dimethoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(3-isopropoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(4-cyclopentyloxy-phenyl)-2-methoxy-acetamide hydrochloride,

(RS)-N-(4-Carbamimidoyl-benzyl)-2-(4-isopropoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-{4-[(4-Carbamimidoyl-benzylcarbamoyl)-methoxy-methyl]-phenoxy}-acetic acid methyl ester hydrochloride,
(RS)-{4-[(4-Carbamimidoyl-benzylcarbamoyl)-methoxy-methyl]-phenoxy}-acetic acid,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-[3-(tetrahydro-pyran-4-yloxy)-phenyl]-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(3,5-diethoxy-2-fluoro-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-[5-ethoxy-2-fluoro-4-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(3,4-diethoxy-2-fluoro-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-2-fluoro-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-3-fluoro-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-2-(2,4-Bis-trifluoromethyl-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-[4-(N-Hydroxycarbamimidoyl)-benzyl]-2-(2-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide actetate,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-5-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2,3-difluoro-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2,6-difluoro-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-2-(4-Bromo-2-fluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
(RS)-2-(4-Bromo-2-fluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-acetamide hydrochloride,
(RS)-2-(4-Bromo-2-fluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-propoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-trifluoromethyl-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-[4-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-

acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(4-dimethylamino-phenyl)-2-methoxy-acetamide hxdrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-(4-pyrrolidin-1-yl-phenyl)-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-chloro-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-2-(4-Acetylamino-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
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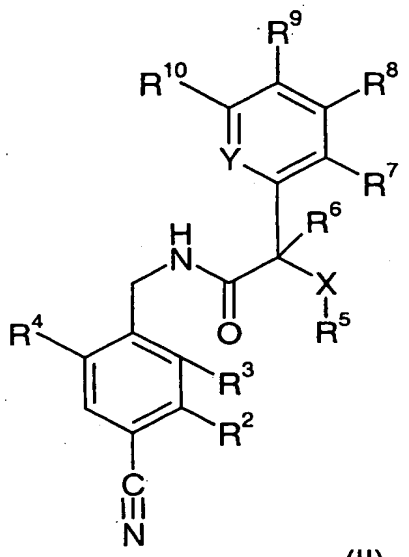
benzyl]-acetamide,
(RS)-4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methoxy-2-oxo-propylamino]-benzamidine hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-chloro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2,6-difluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-propoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-naphthalen-1-yl-propionamide hydrochloride,
(RS)-2-(4-Bromo-2,6-difluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-isopropoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-isobutoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-{2-fluoro-4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-pyridin-3-yl-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-pyridin-4-yl-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-2-(5-Bromo-2-fluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(4-fluoro-biphenyl-3-yl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-5-methyl-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-5-trifluoromethyl-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-6-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-6-hydroxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-dimethylamino-2-phenyl-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methylamino-2-phenyl-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methylsulfanyl-2-phenyl-acetamide hydrochloride,

(RS)-N-(4-Carbamimidoyl-benzyl)-2-ethylsulfanyl-2-phenyl-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methanesulfonyl-2-phenyl-acetamide hydrochloride,
(RS)-2-Amino-N-(4-carbamimidoyl-benzyl)-2-phenyl-acetamide hydrochloride,
(RS)-2-Acetylamino-N-(4-carbamimidoyl-benzyl)-2-phenyl-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-[2-fluoro-4-(2-phenoxy-ethoxy)-phenyl]-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-pyridin-2-yl-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-phenyl-propionamide hydrochloride,
(RS)-2-(4-Bromo-2,6-difluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-acetamide hydrochloride,
N-(4-Carbamimidoyl-benzyl)-2-[2-fluoro-6-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide hydrochloride, and
N-(4-Carbamimidoyl-benzyl)-2-(2-carbamoylmethoxy-6-fluoro-phenyl)-2-methoxy-acetamide hydrochloride,
and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of formula (I) are those selected from the group consisting of
(S)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-phenyl-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-[Amino-(4-{[2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetylamino]-methyl}-phenyl)-methylene]-carbamic acid ethyl ester,
(RS)-2-(2-Fluoro-4-methoxy-phenyl)-N-[4-(N-hydroxycarbamimidoyl)-benzyl]-2-methoxy-acetamide,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(3-fluoro-3'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-ethoxy-2-(2-fluoro-4-methoxy-phenyl)-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2,6-difluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-pyridin-3-yl-phenyl)-2-methoxy-acetamide hydrochloride, and
(RS)-2-(4-Bromo-2,6-difluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-acetamide hydrochloride,
and pharmaceutically acceptable salts thereof.

It will be appreciated that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

The invention further relates to a process for the manufacture of compounds of formula (I) as defined above, which process comprises converting the nitrile group in a compound of formula (II)



(II)

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X and Y have the significances given above, into a carbamimidoyl group, or into a N-hydroxy-carbamimidoyl group, or into a N-amino-carbamimidoyl group, and, if desired, converting an obtained compound of formula (I) into a pharmaceutically acceptable salt. A preferred process as described above comprises the conversion of the nitrile group into a carbamamidoyl group, or into a N-hydroxy-carbamimidoyl group, or into a N-amino-carbamimidoyl group.

The conversion of the nitrile group in a compound of formula II into a carbamimidoyl group $-C(NH)NH_2$ or into a N-hydroxy-carbamimidoyl group $-C(NOH)NH_2$ group or into a N-amino-carbamimidouyl group $-C(N-NH2)NH_2$ can be carried out according to methods known per se. For example, the conversion into a N-hydroxy-carbamimidoyl group can be performed by dissolving a compound of formula II in a solvent, such as DMF, ethanol or methanol, treating the solution with hydroxylamine or a salt of hydroxylamine with an inorganic acid, such as hydroxylamine hydrochloride, and thereafter with a base, such as diisopropylethylamine or triethylamine, sodium hydride or sodium methanolate, conveniently at a temperature up to 80°C.

The conversion of the nitrile group into a carbamimidoyl group can be carried out e.g. by treating a compound of formula II in a solvent, such as ethanol or methanol, or a solvent mixture, such as chloroform and methanol or chloroform and ethanol, with a dry stream of hydrogen chloride, conveniently at a temperature below 10 °C. The solution containing the iminoether can be evaporated and the residue can be treated with gaseous

ammonia or an ammonium salt in methanol or ethanol. In an analogous manner, the iminoether can be converted into a N-hydroxy-carbamimidoyl compound of formula I with hydroxylamine or a salt thereof in the presence of a base or into a N-amino-carbamimidoyl compound of formula I with hydrazine or a salt thereof in the presence of a base. In so doing, other reactive groups present in the compound of formula I and reactive towards the treatment wih hydrogen chloride or gaseous ammonia or ammonium chloride or hydroxylamine or hydrazine can be modified. For example, in the case of treatment with hydrogen chloride a benzyloxy group R^7, R^8, R^9, R^{10} or R^{11} can be converted into the hydroxy group. In the case of treatment with gaseous ammonia in methanol or ethanol a lower-alkoxy-carbonyl-lower-alkoxy group R^7, R^8, R^9, R^{10} or R^{11} can be converted into a carbamoyl-lower-alkoxy group.

If a carbamimidoyl compound of formula (I) is obtained from a nitrile of formula (II) by treatment with hydrogen chloride and subsequent reaction with gaseous ammonia or ammonium chloride, the carbamimidoyl product is obtained as hydrochloride salt. This salt can be converted into any other pharmaceutically acceptable salt by chromatography over a adequately charged basic ion exchange resin. Alternatively the hydrochloride salt of a carbamimidoyl compound of formula (I) can be converted into the corresponding free base by treatment with sodium ethanolate in ethanol and subsequently treated with an excess of an appropriate acid to generate any pharmaceutically acceptable salt.

Any pharmaceutically acceptable salt of a carbamimidoyl compound of formula (I) can furthermore be obtained when a N-hydroxy-carbamimidoyl compound of formula (I) is hydrogenated in a solvent like ethanol, methanol, dioxan or THF, with hydrogen and a catalyst such as palladium, platinum or nickel in the presence of an appropriate acid.

Functional groups in compounds of formula (I) can be modified. As modifications of functional groups in a compound of formula I there come into consideration especially the conversion of a N-hydroxy-carbamimidoyl group into a carbamimidoyl group, the esterification of a carboxy group, the saponification of an ester group and the cleavage of an ether group, such as an arylalkyl ether group, e.g. the benzyl ether group. All of these reactions can be carried out according to methods known per se.

A compound of formula (I) in which R^1 represents a hydroxy group can be converted into a compound of formula (I) in which R^1 represents hydrogen by hydrogenation in a solvent, such as ethanol, methanol, dioxan, THF or glacial acetic acid, or a solvent mixture, such as ethanol and glacial acetic acid, with hydrogen and a catalyst, such as palladium, platinum or nickel. In so doing, other reactive groups present in the compound of formula I and reactive towards the reducing agent can be modified.

A compound of formula (I) in which R^1 represents lower-alkoxy-carbonyl is obtained by reacting a compound of formula (I) in which R^1 represents hydrogen with a chloroformic acid lower alkyl ester in a solvent, such as dichloromethane, dioxan or DMF, or a solvent mixture, such as dichloromethane and water or ethyl acetate and water, in the presence of an organic base, such as pyridine or triethylamine, or an inorganic base, such as sodium hydroxide, sodium carbonate or potassium hydrogen carbonate.

A compound of formula (I) in which R^1 represents lower-alkyl-carbonyl or aryl-carbonyl is obtained by reacting a compound of formula (I) in which R^1 represents hydrogen with a acyl chloride in a solvent, such as dichloromethane, dioxan or DMF, or a solvent mixture, such as dichloromethane and water or ethyl acetate and water, in the presence of an organic base, such as pyridine or triethylamine, or an inorganic base, such as sodium hydroxide, sodium carbonate or potassium hydrogen carbonate.

A compound of formula (II) in which R^7, R^8, R^9, R^{10} or R^{11} has the significance of a hydroxy group can be reacted:

- with an alkylating agent such as an appropriately substituted alkyl bromide, alkyl iodide or alkyl mesylate in the presence of a base such as potassium carbonate or caesium carbonate in a solvent such as DMF or acetone, or

- by a Mitsunobu reaction with an appropriately substituted alcohol in the presence of DEAD, DIAD, or di-tert.-butyl-azodicarboxylate, and triphenylphosphine in a solvent such as THF or dioxane, or

- by reaction with trifluorosulfonic acid anhydride and an organic base like triethylamine in a solvent such as THF or dichloromethane. The trifluorosulfonic acid ester thus obtained is further converted by reaction with an appropriately substituted alkine in the presence of an organic base as triethylamine and copper(I)iodide in a solvent as DMF and a palladium catalyst as tetrakis(triphenylphosphin)palladium(0)

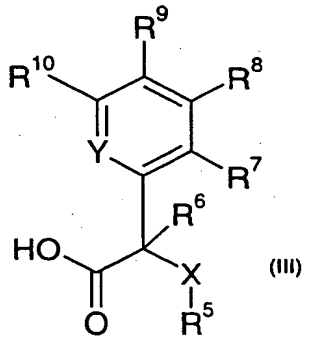
Furthermore, a compound of formula (II) in which R^7, R^8, R^9, R^{10} or R^{11} has the significance of a bromide can be reacted

- with a aryl boronic acid or a heteroaryl boronic acid in the presence of a base as solid or aqueous potassium carbonate or sodium carbonate and a palladium catalyst such as tetrakis(triphenylphosphin)palladium(0) or 1,1′-bis(diphenyl-phosphin) ferrocene-palladium dichloride in a solvent such as toluene or THF, or

- with bis(pinacolato)diboron in the presence of a base like potassium acetate and a palladium catalyst like bis(triphenylphosphine)palladium(II) chloride and a solvent

such as dioxane. The boronic acid ester thus obtained is further converted by reaction with an arylhalogenide or a heteroaryl halogenide and a base like solid or aqueous potassium carbonate or sodium carbonate and a palladium catalyst such as bis(diphenylphosphin)ferrocene-palladium dichloride in a solvent such as 1,2-dimethoxyethane.

The compounds of formula (II) in which X has the significance of an oxygen is prepared according to general methods known per se, e.g.by coupling of an acid of formula (III) and an appropriately substituted 4-aminomethyl benzonitrile in the presence of coupling reagents as BOP or EDCI/HOBt and a organic base such as triethylamine or diisopropyl ethyl amine in a solvent such as THF.

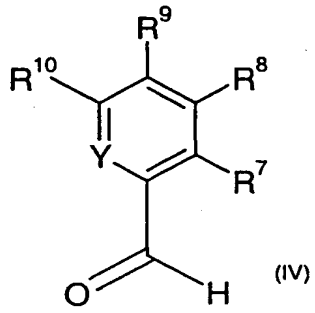


(III)

Compounds of formula (III) in which X has the significance of oxygen are known per se or can be prepared according to general methods known per se, e.g. as described hereinafter and/or as described in the the Examples or in analogy to these methods.

For example, a compound of formula (III) in which X has the significance of oxygene and R^6 has the significance of hydrogen can be prepared

- by reaction of an aldehyde of formula (IV) with bromoform or chloroform in a mixture of solvents like dioxane/methanol or dioxane/ethanol in the presence of an inorganic base like sodium hydroxide or potassium hydroxide, or
- by reaction of an aldehyde of formula (IV) with trimethylsilyl cyanide in the presence of ZnI_2 in a solvent such as dichloromethane. The trimethylsilyl cyanohydrine thus obtained is subsequently hydrolysed in concentrated hydrochloric acid to the corresponding α-hydroxy carboxylic acid which is then alkylated to give a compound of formula (III) using an appropiately substituted alkyl halide in the presence of silver oxide in a solvent such as toluene.



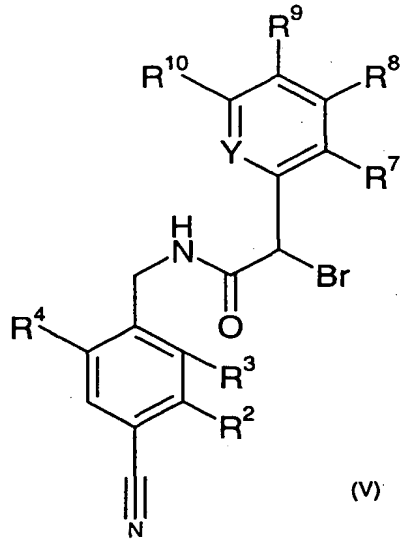
(IV)

Compounds of formula (IV) are known per se or can be prepared according to general methods known per se, e.g. as described hereinafter and/or as described in the Examples or in analogy to these methods.

A compound of formula (III) in which X has the significance of oxygene and R^6 has the significance of methyl can be prepared by reaction of an appropriately substituted acetophenon with bromoform or chloroform in a mixture of solvents like dioxane/methanol or dioxane/ethanol in the presence of a inorganic base like sodium hydroxide or potassium hydroxide.

The compounds of formula (II) in which X has the significance of an NR^{12} and R^{12} has the significance of lower-alkyl are prepared according to general methods known per se, e.g. as described hereinafter and/or as described in the Examples or in analogy to these methods.

For example, a compound of formula (V)



(V)

can be reacted with an lower-alkyl amine or a di-lower-alkyl amine or the corresponding ammonium hydrochlorides in the presence of an organic base as triethylamine and a catalyst such as tetrabutylammonium iodide in a solvent as THF.

Compounds of formula (II) in which X has the significance of NR^{12} and R^{12} has the significance of lower-alkyl-carbonyl can be obtained by coupling an appropriately substituted N-Boc-phenylglycine and an appropriately substituted 4-aminomethyl benzonitrile in the presence of coupling reagents such as BOP or EDCI/HOBt and an organic base as triethylamine or diisopropyl ethyl amine in a solvent such as THF. The Boc group can be cleaved by reaction with trifluoroacetic anhydride in a solvent like dichloromethane. The amino group thus liberated can then be reacted with an appropriately substituted acyl chloride or acyl anhydride in the presence of an organic amine like triethylamine in a solvent like THF or dichloromethane.

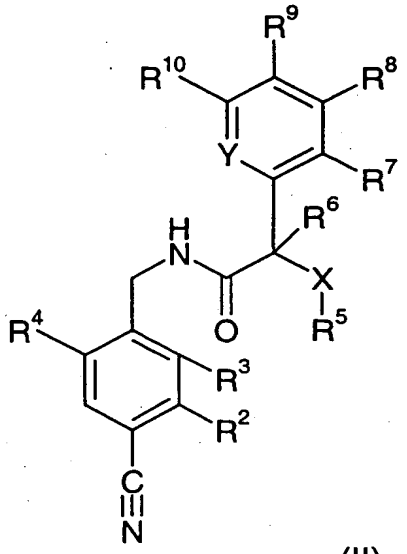
The compounds of formula (II) in which X has the significance of sulfur are prepared according to general methods known per se, e.g. as described hereinafter and/or as described in the Examples or in analogy to these methods. For example, a compound of formula (V) can be reacted with the sodium salt of a lower-alkyl mercaptane in the presence of a catalyst such as tetrabutylammonium iodide in a solvent such as methanol.

Compounds of formula (II) in which X has the significance of SO_2 can be obtained from compounds of formula (II) in which X has the significance of sulfur by reaction with an oxidant such as m-chloro perbenzoic acid in a solvent like dichloromethane.

Compounds of formula (V) can be obtained by coupling an appropriately substituted α-bromo-phenylacetic acid and an appropriately substituted 4-aminomethyl benzonitrile in the presence of coupling reagents as BOP or EDCI/HOBt and an organic base as triethylamine or diisopropyl ethyl amine in a solvent such as THF.

Insofar as their preparation is not described in the examples, the compounds of formulae (I), (II), (III), (IV) and (V) can be prepared according to analogous methods or according to the methods set forth above.

Furthermore, the invention relates to compounds of formula (I) as defined above, when manufactured by a process as described above. In another embodiment, the invention relates to the intermediates, the compounds of formula (II)



(II)

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X and Y have the significances given above.

As described above, the compounds of formula (I) are active compounds and inhibit the formation of coagulation factors Xa, IXa and thrombin induced by factor VIIa and tissue factor or are derivatives which are converted under physiological conditions to such active compounds. These compounds consequently influence both platelet aggregation which is induced by these factors and plasmatic blood coagulation. They therefore inhibit the formation of thrombi and can be used for the treatment and/or prevention of diseases, such as arterial and venous thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation and arteriosclerosis. Furthermore, these compounds have an effect on tumour cells and prevent metastases. They can therefore also be used as antitumour agents. Prevention and/or treatment thrombosis, particularly arterial or deep vein thrombosis, is the preferred indication.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of diseases which are associated with the formation of clotting factors Xa, IXa and thrombin induced by factor VIIa and tissue factor, particularly as therapeutically active substances for the treatment and/or prophylaxis of arterial and venous thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation, arteriosclerosis and/or tumour.

In another preferred embodiment, the invention relates to a method for the therapeutic and/or prophylactic treatment of diseases which are asscociated with the formation of clotting factors Xa, IXa and thrombin induced by factor VIIa and tissue factor, particularly for the therapeutic and/or prophylactic treatment of arterial and venous thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation, arteriosclerosis and/or tumour, which method comprises administering a compound as defined above to a human being or animal.

The invention also embraces the use of compounds as defined above for the therapeutic and/or prophylactic treatment of diseases which are asscociated with the formation of clotting factors Xa, IXa and thrombin induced by factor VIIa and tissue factor, particularly for the therapeutic and/or prophylactic treatment of arterial and venous

thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation, arteriosclerosis and/or tumour.

The invention also relates to the use of compounds as described above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are asscociated with the formation of clotting factors Xa, IXa and thrombin induced by factor VIIa and tissue factor, particularly for the therapeutic and/or prophylactic treatment of arterial and venous thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation, arteriosclerosis and/or tumour. Such medicaments comprise a compound as described above.

The inhibition of the amidolytic activity of factor VIIa/tissue factor complex by the compounds in accordance with the invention can be demonstrated with the aid of a chromogenic peptide substrate as described hereinafter.

The measurements were carried out by an automated robotic assay on microtitre plates at room temperature. To this end, 100 µl of a solution of 26 nM of tissue factor, 9 nM of soluble factor VIIa and 8 mM of calcium chloride were added to 25 µl of a solution of the inhibitor in a buffer [pH 7.5, 100 mM, comprising 0.14M NaCl, 0.1M N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulphonic acid) (HEPES), 0.5 mg/l of fatty-acid-free BSA (bovine serum albumin) and 0.05% NaN_3] in each well of the plate. After an incubation time of 15 minutes the reaction was started by the addition of 50 µl of chromogenic substrate Chromozym-tPA (3.5 mM, $MeSO_2$-D-Phe-Gly-Arg-paranitroanilide) and the hydrolysis of the substrate was followed spectrophotometrically on a kinetic microtitre plate reader over 10 minutes. Using the plot of the inhibition curves, the Ki values were determined according to the method described in Biochem. J. 55, 1953, 170-171.

The activity of the low molecular weight substances can, moreover, be characterized in the "prothrombin time" (PT) clotting test. The substances are prepared as a 10 mM solution in DMSO or DMSO/0.1M HCl (DHCl) and thereafter made up to the desired dilution in the same solvent. Thereafter, 0.25 ml of human plasma (obtained from whole blood anticoagulated with 1/10 volume of 108 mM Na citrate) was placed in the instrument-specific sample container. In each case 5 µl of each dilution of the substance-dilution series was then mixed with the plasma provided. This plasma/inhibitor mixture was incubated at 37°C for 2 minutes. Thereafter, there were pipetted to the semi-automatic device (ACL, Automated Coagulation Laboratory (Instrument Laboratory)) 50 µl of plasma/ inhibitor mixture in the measurement container. The clotting reaction was initiated by the addition of 0.1 ml of Innovin® (recombinant human tissue factor combined with calcium buffer and synthetic phospholipids(Dade Behring®, Inc.). The time up to the fibrin cross-linking was determined photooptically from the ACL. The inhibitor concentration, which brought about a doubling of the PT clotting time, was determined by means of a graph.

The Ki value of the active compounds of the present invention preferably amounts to about 0.1 to 50 µM, especially about 0.1 to 5 µM. The PT values preferably amount to about 5 to 100 µM, especially to about 5 to 30 µM.

Example	Ki [μM]
24.3	2.21
33.3	0.49
53.3	2.26
72.2	2.10

The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or suspensions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially

about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula I.

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

Abbreviations

BOP = (benzotriazol-1-yloxy)-tris-(dimethylamino)-phosphonium-hexafluorophosphat, CAS = Chemical Abstract Services, DEAD = diethyl azodicarboxylate, DMF = dimethyl formamide, EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, EtOH = ethanol, HOBT = 1-hydroxybenzotriazole, MS = mass spectroscopy, MeOH = methanol, r.t. = room temperature, THF = tetrahydrofuran

General Procedures

General Procedure A: Conversion of an aromatic aldehyde into an aryl-α-alkoxyacetic acid.

To a stirred solution of the aldehyde (1 eq) and bromoform (1.27 eq) in the appropriate alkohol (MeOH or EtOH, 1 ml/mmol aldehyde) and dioxane (1 ml/mmol aldehyde) is added dropwise a solution of potassium hydroxyde (5 eq) in the appropriate alkohol (MeOH or EtOH, 1 ml/mmol aldehyde) for 15 min. For larger amounts a slight cooling is applied. Stirring at r.t. under an argon atmosphere is then continued for 18 – 48 h. The solid is filtered off and washed with the appropriate alkohol. The filtrate is concentrated (rotavapor). The residue is taken up in water. The resulting solution is washed with Et_2O and acidified to pH 1 by dropwise addition of 3.0 N HCl. This is extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated (rotavapor). The crude product can be purified by chromatography (silicagel) or by crystallization.

General Procedure B: Coupling of an aryl-α-alkoxyacetic acid with a primary amine using EDCI as a coupling reagent.

To a stirred solution of the amine (1 eq) in THF is added the acid (1.2 eq), triethylamine (1.2 eq) and EDCI (1.2 eq). HOBT (1.2 eq) can also be added. The mixture is then stirred at r.t. under an argon atmosphere for 16 - 24 h. The mixture is diluted with EtOAc, washed with sat. $KHSO_4$ solution / water (1:1) and water; dried ($MgSO_4$), filtered and concentrated. The crude product can be purified by chromatography (silicagel) or by crystallization.

General Procedure C: Coupling of an aryl-α-alkoxyacetic acid with a primary amine using BOP as a coupling reagent.

To a stirred solution of the amine (1 eq) in THF is added the acid (1.5 eq), N-diisopropylamine (1.5 eq) and BOP-reagent (1.5 eq). The mixture is then stirred at r.t. under an argon atmosphere for 16 - 24 h. The mixture is diluted with EtOAc, washed with

water, 1.0 N NaOH and brine; dried ($MgSO_4$), filtered and concentrated. The crude product can be purified by chromatography (silicagel) or by crystallization.

General Procedure D: Conversion of an aromatic nitrile into an amidine (Pinner reaction).

Dry HCl gas is passed over a cooled (-10°C), stirred solution of the starting material in $CHCl_3$ / EtOH (or MeOH) 5:1 for 15 min. The flask is stoppered and left at 4 °C overnight. If conversion is not complete, the reaction mixture is allowed to warm to r.t. The mixture is concentrated (rotavapor and high vacuum) at r.t. The residue is dissolved in EtOH and treated with a 2.0 M NH_3 solution in EtOH. The resulting mixture is stirred at r.t. (sensitive compounds) or 60°C for 2 – 18 h. The mixture is then concentrated (rotavapor) and purified by chromatography (silicagel).

Example 1

1.1

(S)-(+)-Methoxyphenylacetic acid was coupled with 4-aminomethyl benzonitrile (CAS No: 10406-25-4) according to general procedure C to give (S)-N-(4-cyano-benzyl)-2-methoxy-2-phenyl-acetamide as an off-white solid. MS 281.2 ($[M+H]^+$)

1.2

(S)-N-(4-Cyano-benzyl)-2-methoxy-2-phenyl-acetamide was converted to (S)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-phenyl-acetamide hydrochloride according to general procedure D. Colorless solid. MS 298 ($[M+H]^+$)

Example 2

2.1

(R)-(+)-Methoxyphenylacetic acid was coupled with 4-aminomethyl benzonitrile (CAS No: 10406-25-4) according to general procedure C to give (R)-N-(4-cyano-benzyl)-2-methoxy-2-phenyl-acetamideas an off-white solid. MS 281.1 ($[M+H]^+$)

2.2

(R)-N-(4-Cyano-benzyl)-2-methoxy-2-phenyl-acetamide was converted to (R)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-phenyl-acetamide hydrochloride according to general procedure D. Colorless solid. MS 298.2 ($[M+H]^+$)

Example 3

3.1

4-Benzyloxybenzaldehyde was converted to (RS)-(4-benzyloxy-phenyl)-methoxy-acetic acid according to general procedure A. Off-white solid. MS 271.1 ($[M-H]^-$)

3.2

(RS)-(4-Benzyloxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile to give (RS)-2-(4-benzyloxy-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide according to general procedure B. Colorless solid. MS 387.3 ($[M+H]^+$)

3.3

(RS)-2-(4-Benzyloxy-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-(4-benzyloxy-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 404.5 ($[M+H]^+$)

Example 4

4.1

4-Phenoxybenzaldehyde was converted to (RS)-methoxy-(4-phenoxy-phenyl)-acetic acid according to general procedure A. Yellow oil. MS 257.0 ($[M-H]^-$)

4.2

(RS)-Methoxy-(4-phenoxy-phenyl)-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-(4-phenoxy-phenyl)-acetamide. Colorless solid. MS 373.3 ($[M+H]^+$)

4.3

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(4-phenoxy-phenyl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(4-phenoxy-phenyl)-acetamide hydrochloride according to general procedure D. Colorless foam. MS 390.3 ($[M+H]^+$)

Example 5

5.1

3-Phenoxybenzaldehyde was converted to (RS)-methoxy-(3-phenoxy-phenyl)-acetic acid according to general procedure A. Light yellow liquid.

5.2

(RS)-Methoxy-(3-phenoxy-phenyl)-acetic acid was coupled with 4-aminomethyl

benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-(3-phenoxy-phenyl)-acetamide. Light yellow oil. MS 373.3 ($[M+H]^+$)

5.3

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(3-phenoxy-phenyl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(3-phenoxy-phenyl)-acetamide hydrochloride according to general procedure D. Colorless amorphous solid. MS 390.3 ($[M+H]^+$)

Example 6

6.1

Benzaldehyde was converted to (RS)-ethoxy-phenyl-acetic acid according to general procedure A. Light yellow liquid.

6.2

(RS)-Ethoxy-phenyl-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-ethoxy-2-phenyl-acetamide. Light yellow semisolid. MS 295.3 ($[M+H]^+$)

6.3

(RS)-N-(4-Cyano-benzyl)-2-ethoxy-2-phenyl-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-2-phenyl-acetamide hydrochloride according to general procedure D. Colorless amorphous solid. MS 312.2 ($[M+H]^+$)

Example 7

7.1

2-Fluorobenzaldehyde was converted to (RS)-(2-fluoro-phenyl)-methoxy-acetic acid according to general procedure A. Off-white amorphous solid. MS 182.9 ($[M-H]^-$)

7.2

(RS)-(2-Fluoro-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-phenyl)-2-methoxy-acetamide. Colorless oil. MS 299.2 ($[M+H]^+$)

7.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 316.2 ($[M+H]^+$)

Example 8

8.1

3-Benzyloxybenzaldehyde was converted to (RS)-(3-benzyloxy-phenyl)-methoxy-acetic acid according to general procedure A. Colorless solid.

8.2

(RS)-(3-Benzyloxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-2-(3-benzyloxy-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Light yellow oil.

8.3

(RS)-2-(3-Benzyloxy-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-(3-benzyloxy-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless amorphous solid. MS 404.5 ($[M+H]^+$)

Example 9

9.1

As a side product of the synthesis of (RS)-2-(3-benzyloxy-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride (example 8.3) there was obtained (RS)-N-(4-carbamimidoyl-benzyl)-2-(3-hydroxy-phenyl)-2-methoxy-acetamide hydrochloride. Colorless amorphous solid. MS 314.2 ($[M+H]^+$)

Example 10

10.1

To a stirred solution of 3-nitrobenzaldehyde (4.043 g) at r.t. in 190 ml CH_2Cl_2 was added ZnI_2 (0.427 g). The mixture was purged with N_2 and cooled to 0°C. Trimethylsilyl cyanide (2.92 g as a solution in 10 ml CH_2Cl_2) was then added dropwise to the mixture for 15 min. The mixture was then allowed to warm to room temperature and stirring was continued for 16 h. Water (250 ml) was then added to the mixture. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (125 ml). The combined organics were washed with water (125 ml) and brine (125 ml), dried ($MgSO_4$), filtered and concentrated (rotavapor) to leave the crude (RS)-(3-nitro-phenyl)-trimethylsilanyloxy-acetonitrile (6.56 g) as an orange oil which was used in the next step without further purification.

10.2

(RS)-(3-Nitro-phenyl)-trimethylsilanyloxy-acetonitrile (6.30 g) was dissolved in concentrated HCl with stirring. The mixture was then refluxed for 3 h. After cooling to

room temperature, the yellow solution was poured into 200 g of crushed ice. This was extracted with Et_2O (150 ml + 150 ml + 150 ml). The combined organics were washed with water (200 ml) and brine (200 ml), dried ($MgSO_4$), filtered and concentrated (rotavapor) to leave a yellow solid. This solid was triturated in a mixture of n-hexane (20 ml) and Et_2O (2 ml), collected by filtration and washed with n-hexane to give (RS)-hydroxy-(3-nitro-phenyl)-acetic acid as a light yellow solid (4.56 g).

10.3

A mixture of (RS)-hydroxy-(3-nitro-phenyl)-acetic acid (1.054 g), Ag_2O (2.478 g) and MeI (2.304 g) was heated to reflux in toluene (10 ml). Stirring was then continued for 3 h. After cooling to r.t., the solid was filtered off and washed with EtOAc. The filtrate was concentrated (rotavapor) to leave the crude (RS)-methoxy-(3-nitro-phenyl)-acetic acid methyl ester (1.161 g) as a light yellow oil.

10.4

A mixture of (RS)-methoxy-(3-nitro-phenyl)-acetic acid methyl ester (1.039 g) and NaOH (0.239 g) in water (0.75 ml) and methanol (10 ml) was stirred at 0°C for 4.5 h. The reaction mixture was then concentrated (rotavapor, high vac.) and the residue (light yellow solid) was taken in water (25 ml). The resulting solution was acidified to pH ~ 1 by dropwise addition of 3.0 N HCl. This was extracted with EtOAc (50 ml + 25 ml). The combined organics were dried (MgSO4), filtered and concentrated (rotavapor) to leave the crude (RS)-methoxy-(3-nitro-phenyl)-acetic acid (0.944 g) as a light yellow solid.

10.5

(RS)-Methoxy-(3-nitro-phenyl)-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-(3-nitro-phenyl)-acetamide. Light yellow gum.

10.6

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(3-nitro-phenyl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(3-nitro-phenyl)-acetamide hydrochloride according to general procedure D. Off-white solid. MS 343.2 ($[M+H]^+$)

Example 11

11.1

4-Biphenylaldehyde was converted to (RS)-biphenyl-4-yl-methoxy-acetic acid according to general procedure A. Light brown solid.

11.2

(RS)-Biphenyl-4-yl-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-2-biphenyl-4-yl-N-(4-cyano-benzyl)-2-methoxy-acetamide. Light yellow solid.

11.3

(RS)-2-Biphenyl-4-yl-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-biphenyl-4-yl-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 374.4 ($[M+H]^+$)

Example 12

12.1

Piperonal was converted to (RS)-benzo[1,3]dioxol-5-yl-methoxy-acetic acid according to general procedure A. Orange oil.

12.2

(RS)-Benzo[1,3]dioxol-5-yl-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-2-benzo[1,3]dioxol-5-yl-N-(4-cyano-benzyl)-2-methoxy-acetamide. Light yellow solid.

12.3

(RS)-2-Benzo[1,3]dioxol-5-yl-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-benzo[1,3]dioxol-5-yl-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride according to general procedure D (Pinner reaction in EtOH/$CHCl_3$ as a solvent). Off-white solid. MS 342.2 ($[M+H]^+$)

Example 13

13.1

As a side product of the synthesis of (RS)-2-benzo[1,3]dioxol-5-yl-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride (example 12.3) there was obtained (RS)-2-benzo[1,3]dioxol-5-yl-N-(4-carbamimidoyl-benzyl)-2-ethoxy-acetamide hydrochloride. Light brown solid. MS 356.3 ($[M+H]^+$)

Example 14

14.1

5-Ethoxy-2-fluoro-3-(1-methyl-piperidin-4-yloxy)-benzaldehyde was converted to (RS)-[5-ethoxy-2-fluoro-3-(1-methyl-piperidin-4-yloxy)-phenyl]-methoxy-acetic acid according to general procedure A. Off-white solid. MS 342.2 ($[M+H]^+$)

14.2

(RS)-[5-Ethoxy-2-fluoro-3-(1-methyl-piperidin-4-yloxy)-phenyl]-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-[5-ethoxy-2-fluoro-3-(1-methyl-piperidin-4-yloxy)-phenyl]-2-methoxy-acetamide. Colorless foam. MS 456.5 ($[M+H]^+$)

14.3

(RS)-N-(4-Cyano-benzyl)-2-[5-ethoxy-2-fluoro-3-(1-methyl-piperidin-4-yloxy)-phenyl]-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-[5-ethoxy-2-fluoro-3-(1-methyl-piperidin-4-yloxy)-phenyl]-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 473.5 ($[M+H]^+$)

Example 15

15.1

2-Fluoro-4-methoxybenzaldehyde was converted to (RS)-(2-fluoro-4-methoxy-phenyl)-methoxy-acetic acid according to general procedure A. Light yellow oil. MS 213.4 ($[M-H]^-$)

15.2

(RS)-(2-Fluoro-4-methoxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide. Colorless oil. MS 329.2 ($[M+H]^+$)

15.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 346.4 ($[M+H]^+$)

15.4

(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride (example 15.3, 200 mg) was dissolved in DMF (2.2 ml). The flask was placed in an ice bath. Ethyl chloroformate (58 mg) and triethylamine (160 mg) were added dropwise. The reaction mixture was stirred for 1.5 h at 0 °C. Ethyl acetate (30 ml) and ice water (40 ml) were added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, dried, filtered and evaporated. The product was purified by chromatography (silicagel, ethylacetate) to give (RS)-[amino-(4-{[2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetylamino]-methyl}-phenyl)-methylene]-carbamic acid ethyl ester (218 mg) as a colorless amorphous solid. MS 418.3 ($[M+H]^+$)

15.5

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide (example 15.2, 251 mg) was dissolved in methanol (7 ml).Hydroxylamine hydrochloride (212 mg) and triethylamine (618 mg) were added. The mixture was stirred for 19 h at r.t. The solvent was evaporated. The residue was dissolved in methylene chloride, washed with water, dried and filtered. The solvent was evaporated to give (RS)-2-(2-fluoro-4-methoxy-phenyl)-N-[4-(N-hydroxycarbamimidoyl)-benzyl]-2-methoxy-acetamide (269 mg) as an off-white foam. MS 362.2 ($[M+H]^+$)

15.6

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide (example 15.2, 285 mg) was dissolved in methanol (0.7 ml) and chloroform (3.3 ml). The mixture was placed in an ice-NaCl bath. Dry HCl gas was passed over the reaction mixture for 15 min. The flask was stoppered and left overnight at 4 °C. The mixture was concentrated (rotavapor and high vacuum) at r.t. The residue was dissolved in methanol (1.9 ml). Hydrazine hydrochloride (66 mg) and triethylamine (264 mg) were added. The mixture was stirred overnight. The solvent was evaporated and the product was purified by chromatography (silica gel, CH_2Cl_2 => CH_2Cl_2/MeOH 4:1) to give RS)-2-(2-fluoro-4-methoxy-phenyl)-N-[4-(N-aminocarbamimidoyl)-benzyl]-2-methoxy-acetamide (205 mg) as an off-white foam. MS 361.2 ($[M+H]^+$)

Example 16

16.1

3-Benzyloxy-4-methoxy-benzaldehyde was converted to (RS)-(3-benzyloxy-4-methoxy-phenyl)-methoxy-acetic acid according to general procedure A. Orange solid.

16.2

To a stirred solution of (RS)-(3-benzyloxy-4-methoxy-phenyl)-methoxy-acetic acid (0.923 g) at r.t. in ethanol was added 10% Pd/C. The mixture was then stirred at r.t. under a hydrogen atmosphere for 17 h. The catalyst was filtered off and washed with dichloromethane. The filtrate was concentrated (rotavapor) to give (RS)-(3-hydroxy-4-methoxy-phenyl)-methoxy-acetic acid (0.642 g) as an orange gum.

16.3

(RS)-(3-Hydroxy-4-methoxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(3-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide. White foam.

16.4

To a stirred solution of (RS)-N-(4-cyano-benzyl)-2-(3-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide (0.303 g) at r.t. in DMF (3 ml) were added K_2CO_3 (0.14 g) and ethyl bromoacetate (0.169 g). The reaction mixture was then stirred at r.t. under an argon atmosphere for 5 h 45. The mixture was diluted with EtOAc (25 ml), washed with water (25 ml) and brine (25 ml), dried ($MgSO_4$), filtered and concentrated (rotavapor) to leave the crude product as a light yellow gum. The product was purified by chromatography (Silicagel (20 g) using a gradient profile: cyclohexane to cyclohexane / EtOAc 35:65) to give (RS)-{5-[(4-cyano-benzylcarbamoyl)-methoxy-methyl]-2-methoxy-phenoxy}-acetic acid ethyl ester (0.342 g) as a white solid.

16.5

(RS)-{5-[(4-Cyano-benzylcarbamoyl)-methoxy-methyl]-2-methoxy-phenoxy}-acetic acid ethyl ester was converted to (RS)-{5-[(4-carbamimidoyl-benzylcarbamoyl)-methoxy-methyl]-2-methoxy-phenoxy}-acetic acid methyl ester hydrochloride according to general procedure D. Off-white solid. MS 416.3 ($[M+H]^+$)

Example 17

17.1

As a side product of the synthesis of (RS)-{5-[(4-carbamimidoyl-benzylcarbamoyl)-methoxy-methyl]-2-methoxy-phenoxy}-acetic acid methyl ester hydrochloride (example 16.5) there was obtained (RS)-N-(4-carbamimidoyl-benzyl)-2-(3-carbamoylmethoxy-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride. Off-white solid. MS 401.5 ($[M+H]^+$)

Example 18

18.1

3-Benzyloxy-4-methoxy-benzaldehyde was converted to (RS)-(3-benzyloxy-4-methoxy-phenyl)-ethoxy-acetic acid according to general procedure A. Light yellow solid.

18.2

To a stirred solution of (RS)-(3-benzyloxy-4-methoxy-phenyl)-ethoxy-acetic acid (0.801 g) at r.t. in ethanol was added 10% Pd/C (0.1 g). The mixture was then stirred at r.t. under a hydrogen atmosphere for 17 h. The catalyst was filtered off and washed with dichloromethane. The filtrate was concentrated (rotavapor). The residue was purified by chromatography to give (RS)-ethoxy-(3-hydroxy-4-methoxy-phenyl)-acetic acid (0.250 g) as a light yellow gum.

18.3

(RS)-Ethoxy-(3-hydroxy-4-methoxy-phenyl)-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-ethoxy-2-(3-hydroxy-4-methoxy-phenyl)-acetamide. Light yellow gum.

18.4

To a stirred solution of (RS)-N-(4-cyano-benzyl)-2-ethoxy-2-(3-hydroxy-4-methoxy-phenyl)-acetamide (0.158 g) at r.t. in DMF (1.5 ml) were added K_2CO_3 (0.067 g) and ethyl bromoacetate (0.081 g). The reaction mixture was then stirred at r.t. under an argon atmosphere for 24 h. The mixture was diluted with EtOAc (10 ml), washed with water (10 ml+10 ml) and brine (10 ml), dried ($MgSO_4$), filtered and concentrated (rotavapor). The product was purified by chromatography (Silicagel (20 g) using a gradient profile: cyclohexane to cyclohexane / EtOAc 45:55) to give (RS)-{5-[(4-cyano-benzylcarbamoyl)-ethoxy-methyl]-2-methoxy-phenoxy}-acetic acid ethyl ester (0.160 g) as a colorless gum.

18.5

(RS)-{5-[(4-Cyano-benzylcarbamoyl)-ethoxy-methyl]-2-methoxy-phenoxy}-acetic acid ethyl ester was converted to (RS)-{5-[(4-carbamimidoyl-benzylcarbamoyl)-ethoxy-methyl]-2-methoxy-phenoxy}-acetic acid ethyl ester hydrochloride according to general procedure D. Off-white solid. MS 444.4 ($[M+H]^+$)

Example 19

19.1

As a side product of the synthesis of (RS)-{5-[(4-carbamimidoyl-benzylcarbamoyl)-ethoxy-methyl]-2-methoxy-phenoxy}-acetic acid ethyl ester hydrochloride (example 18.5) there was obtained (RS)-N-(4-carbamimidoyl-benzyl)-2-(3-carbamoylmethoxy-4-methoxy-phenyl)-2-ethoxy-acetamide hydrochloride. Off-white solid. MS 415.4 ($[M+H]^+$)

Example 20

20.1

To a stirred suspension of (RS)-{5-[(4-carbamimidoyl-benzylcarbamoyl)-ethoxy-methyl]-2-methoxy-phenoxy}-acetic acid ethyl ester hydrochloride (example 18.5, 0.045 g) at r.t. in THF (1 ml) and water (0.5 ml) was added 1.0 N NaOH (0.2 ml). The mixture was then stirred at r.t. under an argon atmosphere for 3 h. The mixture waa acidified to pH 5-6 by addition of 1.0 N HCl. The THF was removed (rotavapor) and the product precipitated out from the remaining water. It was collected by filtration, washed with water and cyclohexane and dried overnight under high vacuum to give (RS)-{5-[(4-carbamimidoyl-

benzylcarbamoyl)-ethoxy-methyl]-2-methoxy-phenoxy}-acetic acid (0.027 g) as a white powder. MS 416.3 ($[M+H]^+$)

Example 21

21.1

(RS)-(4-Benzyloxy-phenyl)-methoxy-acetic acid (example 3.1) was hydrogenated at r.t. and normal pressure using 10% Pd/C as a catalyst and EtOH as a solvent to give (RS)-(4-hydroxy-phenyl)-methoxy-acetic acid as a light grey solid. MS 181.4 ($[M-H]^-$)

21.2

(RS)-(4-Hydroxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(4-hydroxy-phenyl)-2-methoxy-acetamide. Colorless foam. MS 295.2 ($[M-H]^-$)

21.3

In analogy to example 16.4, (RS)-N-(4-cyano-benzyl)-2-(4-hydroxy-phenyl)-2-methoxy-acetamide was alkylated with ethyl iodide / cesium carbonate in DMF to give (RS)-N-(4-cyano-benzyl)-2-(4-ethoxy-phenyl)-2-methoxy-acetamide as a colorless solid. MS 325.3 ($[M+H]^+$)

21.4

(RS)-N-(4-Cyano-benzyl)-2-(4-ethoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-2-(4-ethoxy-phenyl)-acetamid hydrochloride according to general procedure D using EtOH/$CHCl_3$ as a solvent. Off-white amorphous solid. MS 365.3 ($[M+H]^+$)

Example 22

22.1

(RS)-N-(4-Cyano-benzyl)-2-(4-hydroxy-phenyl)-2-methoxy-acetamide (example 21.2, 0.406 g) was dissolved in THF (12 ml). Triphenylphosphine (0.539 g) and 4-hydroxy-N-methylpiperidine (0.237 g) were added. The reaction mixture was cooled to 0 °C. Slowly, DEAD (0.384 g) was added. The reaction mixture was stirred at 0 °C for 30 min and at r.t. for 5 days. The solvent was evaporated and the product was purified by chromatography (silicagel, mobile phase: gradient from CH_2Cl_2 to CH_2Cl_2/MeOH 4:1) to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-[4-(1-methyl-piperidin-4-yloxy)-phenyl]-acetamide as a colorless foam (0.241 g). MS 394.4 ($[M+H]^+$)

22.2

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-[4-(1-methyl-piperidin-4-yloxy)-phenyl]-

acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-[4-(1-methyl-piperidin-4-yloxy)-phenyl]-acetamide hydrochloride according to general procedure D. Colorless foam. MS 411.4 ($[M+H]^+$)

Example 23

23.1

(+/-)-α-Methoxy-alpha-trifluoromethyl phenylacetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionamide. Off-white solid.

23.2

(RS)-N-(4-Cyano-benzyl)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-3,3,3-trifluoro-2-methoxy-2-phenyl-propionamide hydrochloride according to general procedure D. White solid. MS 366.2 ($[M+H]^+$)

Example 24

24.1

6-Fluorveratraldehyde was converted to (RS)-(2-fluoro-4,5-dimethoxy-phenyl)-methoxy-acetic acid according to general procedure A. Light yellow oil. MS 243.1 ($[M-H]^-$)

24.2

(RS)-(2-Fluoro-4,5-dimethoxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4,5-dimethoxy-phenyl)-2-methoxy-acetamide. Red foam. MS 359.2 ($[M+H]^+$)

24.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4,5-dimethoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-4,5-dimethoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Orange solid. MS 376.4 ($[M+H]^+$)

Example 25

25.1

(RS)-(3-Benzyloxy-phenyl)-methoxy-acetic acid (example 8.1) was hydrogenated at r.t. and normal pressure using 10% Pd/C as a catalyst and EtOH as a solvent to give (RS)-(3-hydroxy-phenyl)-methoxy-acetic acid as a colorless foam.

25.2

(RS)-(3-Hydroxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(3-hydroxy-phenyl)-2-methoxy-acetamide. Colorless oil.

25.3

In analogy to example 16.4, (RS)-N-(4-cyano-benzyl)-2-(3-hydroxy-phenyl)-2-methoxy-acetamide was alkylated with 2-iodopropane / cesium carbonate in DMF to give (RS)-N-(4-cyano-benzyl)-2-(3-isopropoxy-phenyl)-2-methoxy-acetamide as a colorless oil. MS 339.2 ($[M+H]^+$)

25.4

(RS)-N-(4-Cyano-benzyl)-2-(3-isopropoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(3-isopropoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless amorphous solid. MS 356.3 ($[M+H]^+$)

Example 26

26.1

In analogy to example 22.1, (RS)-N-(4-cyano-benzyl)-2-(4-hydroxy-phenyl)-2-methoxy-acetamide (example 21.2) was reacted with cyclopentanol, triphenylphosphine and DEAD in THF. Further conversion according to general procedure D gave (RS)-N-(4-carbamimidoyl-benzyl)-2-(4-cyclopentyloxy-phenyl)-2-methoxy-acetamide hydrochloride as a light yellow solid. MS 282.3 ($[M+H]^+$)

Example 27

27.1

In analogy to example 16.4, (RS)-N-(4-cyano-benzyl)-2-(4-hydroxy-phenyl)-2-methoxy-acetamide (example 21.2) was alkylated with 2-iodopropane / cesium carbonate in DMF to give (RS)-N-(4-cyano-benzyl)-2-(4-isopropoxy-phenyl)-2-methoxy-acetamide as a colorless solid. MS 339.2 ($[M+H]^+$)

27.2

(RS)-N-(4-Cyano-benzyl)-2-(4-isopropoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(4-isopropoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 356.3 ($[M+H]^+$)

Example 28

28.1

In analogy to example 16.4, (RS)-N-(4-cyano-benzyl)-2-(4-hydroxy-phenyl)-2-methoxy-acetamide (example 21.2) was alkylated with ethylbromoacetate / cesium carbonate in DMF to give (RS)-{4-[(4-cyano-benzylcarbamoyl)-methoxy-methyl]-phenoxy}-acetic acid ethyl ester as a colorless solid. MS 383.3 ($[M+H]^+$)

28.2

(RS)-{4-[(4-Cyano-benzylcarbamoyl)-methoxy-methyl]-phenoxy}-acetic acid ethyl ester was converted to (RS)-{4-[(4-carbamimidoyl-benzylcarbamoyl)-methoxy-methyl]-phenoxy}-acetic acid methyl ester hydrochloride according to general procedure D using MeOH/$CHCl_3$ as a solvent. Colorless foam. MS 386.3 ($[M+H]^+$)

Example 29

29.1

In analogy to example 20.1, (RS)-{4-[(4-carbamimidoyl-benzylcarbamoyl)-methoxy-methyl]-phenoxy}-acetic acid methyl ester hydrochloride (example 28.2) was hydrolyzed to (RS)-{4-[(4-carbamimidoyl-benzylcarbamoyl)-methoxy-methyl]-phenoxy}-acetic acid. Colorless solid. MS 370.2($[M-H]^-$)

Example 30

30.1

In analogy to example 22.1, (RS)-N-(4-cyano-benzyl)-2-(3-hydroxy-phenyl)-2-methoxy-acetamide (example 25.2) was reacted with tetrahydro-2*H*-pyran-4-ol, DEAD and triphenylphosphine in THF and subsequently converted into (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-[3-(tetrahydro-pyran-4-yloxy)-phenyl]-acetamide hydrochloride according to general procedure D. Colorless amorphous solid. MS 398.4 ($[M+H]^+$)

Example 31

31.1

3,5-Diethoxy-2-fluoro-benzaldehyde (CAS 277324-21-7) was converted to (RS)-(3,5-diethoxy-2-fluoro-phenyl)-methoxy-acetic acid according to general procedure A. Yellow oil. MS 271.1 ($[M-H]^-$)

31.2

(RS)-(3,5-Diethoxy-2-fluoro-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-

benzyl)-2-(3,5-diethoxy-2-fluoro-phenyl)-2-methoxy-acetamide. Light yellow oil. MS 387.3 ($[M+H]^+$)

31.3

(RS)-N-(4-Cyano-benzyl)-2-(3,5-diethoxy-2-fluoro-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(3,5-diethoxy-2-fluoro-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Light brown foam. MS 404.5 ($[M+H]^+$)

Example 32

32.1

5-Ethoxy-2-fluoro-4-(2-hydroxy-ethoxy)-benzaldehyde (CAS 376600-66-7) was converted to (RS)-[5-ethoxy-2-fluoro-4-(2-hydroxy-ethoxy)-phenyl]-methoxy-acetic acid according to general procedure A. Yellow oil. MS 287.0 ($[M-H]^-$)

32.2

(RS)-[5-Ethoxy-2-fluoro-4-(2-hydroxy-ethoxy)-phenyl]-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-[5-ethoxy-2-fluoro-4-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide. Light yellow oil. MS 403.4 ($[M+H]^+$)

32.3

(RS)-N-(4-Cyano-benzyl)-2-[5-ethoxy-2-fluoro-4-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-[5-ethoxy-2-fluoro-4-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white foam. MS 420.3 ($[M+H]^+$)

Example 33

33.1

3,4-Diethoxy-2-fluoro-benzaldehyde was converted to (RS)-(3,4-diethoxy-2-fluoro-phenyl)-methoxy-acetic acid according to general procedure A. Yellow oil. MS 271.1 ($[M-H]^-$)

33.2

(RS)-(3,4-Diethoxy-2-fluoro-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(3,4-diethoxy-2-fluoro-phenyl)-2-methoxy-acetamide. Colorless solid. MS 387.3 ($[M+H]^+$)

33.3

(RS)-N-(4-Cyano-benzyl)-2-(3,4-diethoxy-2-fluoro-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(3,4-diethoxy-2-fluoro-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 404.5 ($[M+H]^+$)

Example 34

34.1

4-(Bromomethyl)-3-fluorobenzonitrile (CAS 105942-09-4, 21 g) was dissolved in DMF (90 ml). Phthalimide potassium salt (19.64 g) was added and the mixture was stirred for 9 h at 130 °C. After cooling to r.t., the mixture was poured on ice. The solid was filtered off. Ethyl acetate and water were added and extracted with ethyl acetate. The organic phase was washed with water, dried, filtered and evaporated to give a light brown solid (14.1 g, 42 % pure as judged by NMR). This solid was suspended in ethanol (50 ml). A solution of hydrazine in water (24%, 15 ml) was added and the mixture was refluxed for a total of 14 h. The mixture was filtered and the solvent was evaporated. The product was purified by chromatography (silica gel, CH_2Cl_2 => CH_2Cl_2/MeOH 4:1) to give 4-aminomethyl-3-fluoro-benzonitrile (0.63 g) as a brown oil.

34.2

(RS)-(2-Fluoro-4-methoxy-phenyl)-methoxy-acetic acid (example 15.1) was coupled with 4-aminomethyl-3-fluoro-benzonitrile according to general procedure B to give (RS)-N-(4-cyano-2-fluoro-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide. Yellow oil. MS 347.3 ($[M+H]^+$)

34.3

(RS)-N-(4-Cyano-2-fluoro-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-2-fluoro-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white amorphous solid. MS 364.2 ($[M+H]^+$)

Example 35

35.1

(RS)-(2-Fluoro-4-methoxy-phenyl)-methoxy-acetic acid (example 15.1) was coupled with 4-aminomethyl-2-fluorobenzonitrile (CAS 368426-73-7) according to general procedure B to give (RS)-N-(4-cyano-3-fluoro-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide. Light yellow solid. MS 347.3 ($[M+H]^+$)

35.2

(RS)-N-(4-Cyano-3-fluoro-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-3-fluoro-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white amorphous solid. MS 364.2 ($[M+H]^+$)

Example 36

36.1

2,4-Bis-(trifluoromethyl)benzaldehyde was converted to (RS)-(2,4-bis-trifluoromethyl-phenyl)-methoxy-acetic acid according to general procedure A. White solid.

36.2

(RS)-(2,4-Bis-trifluoromethyl-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-2-(2,4-bis-trifluoromethyl-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Colorless gum.

36.3

(RS)-2-(2,4-Bis-trifluoromethyl-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-(2,4-bis-trifluoromethyl-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 434.4 ($[M+H]^+$)

Example 37

37.1

2-Benzyloxy-4-methoxy-benzaldehyde (CAS 32884-23-4) was converted to (RS)-(2-benzyloxy-4-methoxy-phenyl)-methoxy-acetic acid according to general procedure A. Light yellow oil. MS 301.1 ($[M-H]^-$)

37.2

In analogy to example 16.2, (RS)-(2-benzyloxy-4-methoxy-phenyl)-methoxy-acetic acid was hydrogenated to give (RS)-(2-hydroxy-4-methoxy-phenyl)-methoxy-acetic acid. Purple solid. MS 211.0 ($[M-H]^-$)

37.3

(RS)-(2-Hydroxy-4-methoxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(2-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide. Orange amorphous solid. MS 327.3 ($[M+H]^+$)

37.4

In analogy to example 15.5, (RS)-N-(4-cyano-benzyl)-2-(2-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-[4-(N-hydroxycarbamimidoyl)-benzyl]-2-(2-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide. White solid. MS 358.1 ($[M-H]^-$)

37.5

A suspension of (RS)-N-[4-(N-hydroxycarbamimidoyl)-benzyl]-2-(2-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide (240 mg) in ethanol (9 ml) and acetic acid (0.38 ml) was hydrogenated for 7.5 h using 10% Pd/C as a catalyst. The reaction mixture was filtered and the solvent was evaporated. The product was purified by chromatography (silica gel, CH_2Cl_2 => CH_2Cl_2/MeOH 4:1) to give (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-hydroxy-4-methoxy-phenyl)-2-methoxy-acetamide actetate (12 mg) as an off-white, amorphous solid. MS 344.2 ($[M+H]^+$)

Example 38

38.1

2-Fluoro-3-methoxybenzaldehyde was converted to (RS)-(2-fluoro-5-methoxy-phenyl)-methoxy-acetic acid according to general procedure A. Light yellow oil.

38.2

(RS)-(2-Fluoro-5-methoxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-5-methoxy-phenyl)-2-methoxy-acetamide. Colorless gum.

38.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-5-methoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-5-methoxy-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D. White solid. MS 346.2 ($[M+H]^+$)

Example 39

39.1

2,3-Difluorobenzaldehyde was converted to (RS)-(2,3-difluoro-phenyl)-methoxy-acetic acid according to general procedure A. Off-white solid.

39.2

(RS)-(2,3-Difluoro-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(2,3-difluoro-phenyl)-2-methoxy-acetamide. Off-white solid.

39.3

(RS)-N-(4-Cyano-benzyl)-2-(2,3-difluoro-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2,3-difluoro-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D. White solid. MS 334.3 ($[M+H]^+$)

Example 40

40.1

2,6-Difluorobenzaldehyde was converted to (RS)-(2,6-difluoro-phenyl)-methoxy-acetic acid according to general procedure A. Light yellow solid.

40.2

(RS)-(2,6-Difluoro-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(2,6-difluoro-phenyl)-2-methoxy-acetamide. Off-white solid.

40.3

(RS)-N-(4-Cyano-benzyl)-2-(2,6-difluoro-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2,6-difluoro-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D. White solid. MS 334.2 ($[M+H]^+$)

Example 41

41.1

4-Bromo-2-fluorobenzaldehyde was converted to (RS)-(4-bromo-2-fluoro-phenyl)-methoxy-acetic acid according to general procedure A using methanol / dioxane as a solvent. Light yellow oil.

41.2

(RS)-(4-Bromo-2-fluoro-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Light yellow gum.

41.3

(RS)-2-(4-Bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 394.1 ($[M+H]^+$)

Example 42

42.1

4-Bromo-2-fluorobenzaldehyde was reacted according to general procedure A using ethanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-ethoxy-acetamide. Light yellow oil. MS 391.1 ($[M+H]^+$)

42.2

(RS)-2-(4-Bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-ethoxy-acetamide was converted to (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-acetamide hydrochloride according to general procedure D. Off-white foam. MS 408.2 ($[M+H]^+$)

Example 43

43.1

4-Bromo-2-fluorobenzaldehyde was converted to (RS)-(4-bromo-2-fluoro-phenyl)-propoxy-acetic acid according to general procedure A using n-propanol / dioxane as a solvent. Colorless semisolid.

43.2

(RS)-(4-Bromo-2-fluoro-phenyl)-propoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-propoxy-acetamide. Colorless oil. MS 405.3 ($[M+H]^+$)

43.3

(RS)-2-(4-Bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-propoxy-acetamide was converted to (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-propoxy-acetamide hydrochloride according to general procedure D. Colorless solid. MS 423.3 ($[M+H]^+$)

Example 44

44.1

2-Fluoro-4-(trifluoromethyl)benzaldehyde was converted to (RS)-(2-fluoro-4-trifluoromethyl-phenyl)-methoxy-acetic acid according to general procedure A. Light yellow gum.

44.2

(RS)-(2-Fluoro-4-trifluoromethyl-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-trifluoromethyl-phenyl)-2-methoxy-acetamide. Light yellow gum.

44.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4-trifluoromethyl-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-4-trifluoromethyl-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 384.2 ($[M+H]^+$)

Example 45

45.1

In analogy to example 16.4, (RS)-N-(4-cyano-benzyl)-2-(4-hydroxy-phenyl)-2-methoxy-acetamide (example 21.2) was alkylated with bromoethanol/cesium carbonate in DMF to give (RS)-N-(4-cyano-benzyl)-2-[4-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide as a colorless oil. MS 363.1 ($[M+Na]^+$)

45.2

(RS)-N-(4-Cyano-benzyl)-2-[4-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-[4-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 358.2 ($[M+H]^+$)

Example 46

46.1

4-Dimethylaminobenzaldehyde was converted to (RS)-(4-dimethylamino-phenyl)-methoxy-acetic acid according to general procedure A. Light brown foam. MS 208.2 ($[M-H]^-$)

46.2

(RS)-(4-Dimethylamino-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(4-dimethylamino-phenyl)-2-methoxy-acetamide. Off-white solid. MS 324.2 ($[M+H]^+$)

46.3

(RS)-N-(4-Cyano-benzyl)-2-(4-dimethylamino-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(4-dimethylamino-phenyl)-2-methoxy-

acetamide hxdrochloride according to general procedure D. Colorless solid. MS 341.2 ($[M+H]^+$)

Example 47

47.1

3-Oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde (CAS 200195-15-9) was reacted according to general procedure A using methanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetamide. Light yellow solid.

47.2

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetamide hydrochloride according to general procedure D. Off-white solid. MS 369.2 ($[M+H]^+$)

Example 48

48.1

4-(1-Pyrrolidino)benzaldehyde was reacted according to general procedure A using methanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-(4-pyrrolidin-1-yl-phenyl)-acetamide. Off-white solid. MS 350.4 ($[M+H]^+$)

48.2

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(4-pyrrolidin-1-yl-phenyl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(4-pyrrolidin-1-yl-phenyl)-acetamide hydrochloride according to general procedure D. Light red foam. MS 367.2 ($[M+H]^+$)

Example 49

49.1

2-Chlorobenzaldehyde was converted to (RS)-(2-chloro-phenyl)-methoxy-acetic acid according to general procedure A. Light yellow oil. MS 198.9 ($[M-H]^-$)

49.2

(RS)-(2-Chloro-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl

benzonitrile according to general procedure B to give (RS)-2-(2-chloro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Light yellow oil. MS 315.1 ($[M+H]^+$)

49.3

(RS)-2-(2-Chloro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-chloro-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white, amorphous solid. MS 332.2 ($[M+H]^+$)

Example 50

50.1

4-Acetamidbenzaldehyde was converted to (RS)-(4-acetylamino-phenyl)-methoxy-acetic acid according to general procedure A. Yellow, amorphous solid. MS 222.0 ($[M-H]^-$)

50.2

(RS)-(4-Acetylamino-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-2-(4-acetylamino-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Off-white, amorphous solid. MS 338.3($[M+H]^+$)

50.3

(RS)-2-(4-Acetylamino-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-(4-acetylamino-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Orange amorphous solid. MS 355.2 ($[M+H]^+$)

Example 51

51.1

4-(Trifluoromethoxy)benzaldehyde was converted to (RS)-methoxy-(4-trifluoromethoxy-phenyl)-acetic acid according to general procedure A. Light yellow oil. MS 249.3 ($[M-H]^-$)

51.2

(RS)-Methoxy-(4-trifluoromethoxy-phenyl)-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-(4-trifluoromethoxy-phenyl)-acetamide. Light blue semisolid. MS 365.2 ($[M+H]^+$)

51.3

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(4-trifluoromethoxy-phenyl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(4-trifluoromethoxy-

phenyl)-acetamide hydrochloride according to general procedure D. Off-white amorphous solid. MS 382.3 ($[M+H]^+$)

Example 52

52.1

1-(4-Formylphenyl)-1*H*-imidazole was reacted according to general procedure A using methanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(4-imidazol-1-yl-phenyl)-2-methoxy-acetamide. Colorless foam. MS 347.2 ($[M+H]^+$)

52.2

(RS)-N-(4-Cyano-benzyl)-2-(4-imidazol-1-yl-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(4-imidazol-1-yl-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Light yellow solid. MS 364.3 ($[M+H]^+$)

Example 53

53.1

6-Methoxy-2-naphtaldehyde was converted to (RS)-methoxy-(6-methoxy-naphthalen-2-yl)-acetic acid according to general procedure A. Light yellow solid. MS 245.2 ($[M-H]^-$)

53.2

(RS)-Methoxy-(6-methoxy-naphthalen-2-yl)-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-(6-methoxy-naphthalen-2-yl)-acetamide. Off-white foam. MS 361.2 ($[M+H]^+$)

53.3

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(6-methoxy-naphthalen-2-yl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(6-methoxy-naphthalen-2-yl)-acetamide hydrochloride according to general procedure D. Off-white solid. MS 378.3 ($[M+H]^+$)

Example 54

54.1

4-Morpholinobenzaldehyde was reacted according to general procedure A using methanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-

benzyl)-2-methoxy-2-(4-morpholin-4-yl-phenyl)-acetamide. Orange oil. MS 366.2 ([M+H]$^+$)

54.2

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(4-morpholin-4-yl-phenyl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(4-morpholin-4-yl-phenyl)-acetamide hydrochloride according to general procedure D. Orange foam. MS 383.3 ([M+H]$^+$)

Example 55

55.1

2-Morpholinobenzaldehyde was reacted according to general procedure A using methanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-(2-morpholin-4-yl-phenyl)-acetamide. Orange oil.

55.2

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-(2-morpholin-4-yl-phenyl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-(2-morpholin-4-yl-phenyl)-acetamide hydrochloride according to general procedure D. Light brown foam. MS 383.3 ([M+H]$^+$)

Example 56

56.1

4-[3-(Dimethylamino)propoxy] benzaldehyde was reacted according to general procedure A using methanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-[4-(3-dimethylamino-propoxy)-phenyl]-2-methoxy-acetamide. Colorless solid. MS 382.3 ([M+H]$^+$)

56.2

(RS)-N-(4-Cyano-benzyl)-2-[4-(3-dimethylamino-propoxy)-phenyl]-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-[4-(3-dimethylamino-propoxy)-phenyl]-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless solid. MS 399.2 ([M+H]$^+$)

Example 57

57.1

To a stirred solution of (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide (example 41.2, 173 mg) in 1,2-dimethoxyethane (8 ml) were added $PdCl_2$(dppf) (34 mg), an aqueous 10% solution of Na_2CO_3 (2 ml) and 4-dimethylaminophenylboronic acid (378 mg). The mixture was then stirred at 85 °C under an argon atmosphere for 1.5 h. After cooling to r.t. the mixture was diluted with ethyl acetate (15 ml) and washed with water (10 ml). The aqueous layer was extracted with ethyl acetate and the combined organics were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The product was purified by chromatography (silica gel, gradient cyclohexane => cyclohexane / ethyl acetate 2:3) to give (RS)-N-(4-cyano-benzyl)-2-(4'-dimethylamino-3-fluoro-biphenyl-4-yl)-2-methoxy-acetamide (167 mg) as a light yellow solid.

57.2

(RS)-N-(4-Cyano-benzyl)-2-(4'-dimethylamino-3-fluoro-biphenyl-4-yl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(4'-dimethylamino-3-fluoro-biphenyl-4-yl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 435.4 ($[M+H]^+$)

Example 58

58.1

In analogy to example 57.1, (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide (example 41.2) was reacted with 4-methoxyphenylboronic acid to give (RS)-N-(4-cyano-benzyl)-2-(3-fluoro-4'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide. Off-white solid.

58.2

(RS)-N-(4-Cyano-benzyl)-2-(3-fluoro-4'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(3-fluoro-4'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide hydrochloride according to general procedure D. White solid. MS 422.3 ($[M+H]^+$)

Example 59

59.1

In analogy to example 57.1, (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide (example 41.2) was reacted with 2-methoxyphenylboronic acid to give

(RS)-N-(4-cyano-benzyl)-2-(3-fluoro-2'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide. Light yellow gum.

59.2

(RS)-N-(4-Cyano-benzyl)-2-(3-fluoro-2'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(3-fluoro-2'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 422.3 ($[M+H]^+$)

Example 60

60.1

In analogy to example 57.1, ,(RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide (example 41.2) was reacted with phenylboronic acid to give (RS)-N-(4-cyano-benzyl)-2-(3-fluoro-biphenyl-4-yl)-2-methoxy-acetamide. Light yellow gum.

60.2

(RS)-N-(4-Cyano-benzyl)-2-(3-fluoro-biphenyl-4-yl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(3-fluoro-biphenyl-4-yl)-2-methoxy-acetamide hydrochloride according to general procedure D. White solid. MS 392.3 ($[M+H]^+$)

Example 61

61.1

In analogy to example 57.1, ,(RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide (example 41.2) was reacted with 3-methoxyphenylboronic acid to give (RS)-N-(4-cyano-benzyl)-2-(3-fluoro-3'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide. Light yellow gum.

61.2

(RS)-N-(4-Cyano-benzyl)-2-(3-fluoro-3'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(3-fluoro-3'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide hydrochloride according to general procedure D. White solid. MS 422.3 ($[M+H]^+$)

Example 62

62.1

2,2-Dimethylchromane-6-carbaldehyde was converted to (RS)-(2,2-dimethyl-chroman-6-yl)-methoxy-acetic acid according to general procedure A. Light yellow oil. MS 249.1 ($[M-H]^-$)

62.2

(RS)-(2,2-Dimethyl-chroman-6-yl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(2,2-dimethyl-chroman-6-yl)-2-methoxy-acetamide. Off-white semi-solid. MS 365.2 ($[M+H]^+$)

62.3

(RS)-N-(4-Cyano-benzyl)-2-(2,2-dimethyl-chroman-6-yl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2,2-dimethyl-chroman-6-yl)-2-methoxy-acetamide hydrochloride according to general procedure D. Light yellow solid. MS 382.4 ($[M+H]^+$)

Example 63

63.1

2-Fluoro-4-methoxybenzaldehyde was converted to (RS)-ethoxy-(2-fluoro-4-methoxy-phenyl)-acetic acid according to general procedure A using ethanol / dioxane as a solvent. Yellow oil. MS 227.2 ($[M-H]^-$)

63.2

(RS)-Ethoxy-(2-fluoro-4-methoxy-phenyl)-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-ethoxy-2-(2-fluoro-4-methoxy-phenyl)-acetamide. Yellow oil. MS 343.2 ($[M+H]^+$)

63.3

(RS)-N-(4-Cyano-benzyl)-2-ethoxy-2-(2-fluoro-4-methoxy-phenyl)-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-2-(2-fluoro-4-methoxy-phenyl)-acetamide hydrochloride according to general procedure D. Colorless foam. MS 360.3 ($[M+H]^+$)

63.4

In analogy to example 15.5, give (RS)-N-(4-cyano-benzyl)-2-ethoxy-2-(2-fluoro-4-methoxy-phenyl)-acetamide (example 63.2) was converted to (RS)-2-ethoxy-2-(2-fluoro-4-methoxy-phenyl)-N-[4-(N-hydroxycarbamimidoyl)-benzyl]-acetamide. Colorless foam. MS 376.3 ($[M+H]^+$)

Example 64

64.1

3-(Cyclopentyloxy)-4-methoxy-benzaldehyde was converted to (RS)-(3-cyclopentyloxy-4-methoxy-phenyl)-methoxy-acetic acid according to general procedure A. Yellow oil. MS 279.2 ($[M-H]^-$)

64.2

(RS)-(3-Cyclopentyloxy-4-methoxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(3-cyclopentyloxy-4-methoxy-phenyl)-2-methoxy-acetamide. Colorless solid.

64.3

(RS)-N-(4-Cyano-benzyl)-2-(3-cyclopentyloxy-4-methoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-4-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-3-methoxy-2-oxo-propylamino]-benzamidine hydrochloride according to general procedure D. Off-white foam. MS 412.4 ($[M+H]^+$)

Example 65

65.1

2-Chloro-4-methoxybenzaldehyde (CAS No: 54439-75-7) was converted to (RS)-(2-chloro-4-methoxy-phenyl)-methoxy-acetic acid according to general procedure A. Yellow oil. MS 228.9 ($[M-H]^-$)

65.2

(RS)-(2-Chloro-4-methoxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-2-(2-chloro-4-methoxy-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Light yellow oil. MS 345.2 ($[M+H]^+$)

65.3

(RS)-2-(2-Chloro-4-methoxy-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-chloro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 362.2 ($[M+H]^+$)

Example 66

66.1

2,6-Difluoro-4-methoxybenzaldehyde (CAS No: 256417-10-4) was converted to (RS)-(2,6-difluoro-4-methoxy-phenyl)-methoxy-acetic acid according to general procedure A. Yellow oil. MS 230.9 ($[M-H]^-$)

66.2

(RS)-(2,6-Difluoro-4-methoxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(2,6-difluoro-4-methoxy-phenyl)-2-methoxy-acetamide. Light yellow amorphous solid. MS 347.1 ($[M+H]^+$)

66.3

(RS)-N-(4-Cyano-benzyl)-2-(2,6-difluoro-4-methoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2,6-difluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 364.2 ($[M+H]^+$)

Example 67

67.1

2-Fluoro-4-methoxybenzaldehyde was reacted according to general procedure A using n-propanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-propoxy-acetamide. Light yellow oil. MS 357.2 ($[M+H]^+$)

67.2

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-propoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-propoxy-acetamide hydrochloride according to general procedure D. Colorless foam. MS 374.2 ($[M+H]^+$)

Example 68

68.1

2-Methoxy-2-(1-naphtyl)propionic acid was coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-naphthalen-1-yl-propionamide. Colorless foam. MS 345.2 ($[M+H]^+$)

68.2

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-naphthalen-1-yl-propionamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-naphthalen-1-yl-propionamide hydrochloride according to general procedure D. Colorless foam. MS 362.2 ($[M+H]^+$)

Example 69

69.1

A solution of 1-bromo-3,5-difluorobenzene (16.8 g) in THF (180 ml) was cooled to -75 °C under an argon atmosphere. A 2 M solution of lithiumdiisopropylamide in THF / heptane / ethylbenzene (43.1 ml) was slowly added at below -70 °C. The mixture was stirred at -78 °C for 1 h. Dimethylformamide (12.6 ml) was added and the mixture was stirred for 2 h. The cooling bath was removed and the mixture was slowly warmed to r.t. The mixture was

diluted with diethyl ether and washed with 0.5 M HCl. The aqueous phase was extracted with diethyl ether. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed to give the crude 4-bromo-2,6-difluorobenzaldehyde (12.4 g).

The crude aldehyde was reacted according to general procedure A using methanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-2-(4-bromo-2,6-difluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Yellow oil. MS 395.0 ($[M+H]^+$)

69.2

(RS)-2-(4-Bromo-2,6-difluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-(4-bromo-2,6-difluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 412.2 ($[M+H]^+$)

Example 70

70.1

In analogy to example 16.4, 2-fluoro-4-hydroxy-benzaldehyde (CAS-No: 348-27-6) was alkylated with benzylbromide / potassium carbonate in DMF to give 4-benzyloxy-2-fluoro-benzaldehyde. Off-white solid. MS 230.1 ($[M+H]^+$)

70.2

4-Benzyloxy-2-fluoro-benzaldehyde was converted to (RS)-(4-benzyloxy-2-fluoro-phenyl)-methoxy-acetic acid according to general procedure A. White solid. MS 289.1 ($[M-H]^-$)

70.3

(RS)-(4-Benzyloxy-2-fluoro-phenyl)-methoxy-acetic acid was hydrogenated at r.t. and normal pressure using 10% Pd/C as a catalyst and EtOH as a solvent to give (RS)-(2-fluoro-4-hydroxy-phenyl)-methoxy-acetic acid as a light yellow oil. MS 199.2 ($[M-H]^-$)

70.4

(RS)-(2-Fluoro-4-hydroxy-phenyl)-methoxy-acetic acid was coupled with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-hydroxy-phenyl)-2-methoxy-acetamide. White solid. MS 315.1 ($[M+H]^+$)

70.5

In analogy to example 16.4, (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-hydroxy-phenyl)-2-methoxy-acetamide was alkylated with 2-iodopropane and cesium carbonate in DMF to

give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-isopropoxy-phenyl)-2-methoxy-acetamide. Light yellow oil. MS 357.2 ($[M+H]^+$)

70.6

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4-isopropoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-4-isopropoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 374.2 ($[M+H]^+$)

Example 71

71.1

In analogy to example 16.4, (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-hydroxy-phenyl)-2-methoxy-acetamide (example 70.4) was alkylated with 1-iodo-2-methylpropane and cesium carbonate in DMF to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-isobutoxy-phenyl)-2-methoxy-acetamide. Off-white, amorphous solid. MS 371.3 ($[M+H]^+$)

71.2

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4-isobutoxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-4-isobutoxy-phenyl)-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 388.3 ($[M+H]^+$)

Example 72

72.1

In analogy to example 22.1, (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-hydroxy-phenyl)-2-methoxy-acetamide (example 70.4) was reacted with 4-fluorophenethyl alcohol, diethyl azodicarboxylate and triphenyl-phosphine in THF to give (RS)-N-(4-cyano-benzyl)-2-{2-fluoro-4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-2-methoxy-acetamide. Colorless oil. MS 437.3 ($[M+H]^+$)

72.2

(RS)-N-(4-Cyano-benzyl)-2-{2-fluoro-4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-{2-fluoro-4-[2-(4-fluoro-phenyl)-ethoxy]-phenyl}-2-methoxy-acetamide hydrochloride according to general procedure D. Off-white, amorphous solid. MS 454.5 ($[M+H]^+$)

Example 73

73.1

To a stirred solution of (RS)-2-(4-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide (example 41.2, 1.16 g) at r.t. in dioxane were added bis(pinacolato)diboron (1.17 g) and potassium acetate (0.91 g). The mixture was purged with argon and bis(triphenylphosphine)palladium(II) chloride (0.13 g) was added. The mixture was then stirred at 80°C under an argon atmosphere for 18 h. The solids were filtered off and washed with EtOAc. The filtrate was concentrated to leave the crude product as a dark brown oil. The product was isolated by chromatography (silica gel, gradient cyclohexane => cyclohexane/EtOAc 3:2) to give (RS)-N-(4-cyano-benzyl)-2-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2-methoxy-acetamide as brown oil (0.64 g). Brown oil. MS 425.4 ($[M+H]^+$)

73.2

In analogy to example 57.1 (RS)-N-(4-cyano-benzyl)-2-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2-methoxy-acetamide was reacted with 3-bromopyridine to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-pyridin-3-yl-phenyl)-2-methoxy-acetamide. Light brown amorphous solid. MS 376.3 ($[M+H]^+$)

73.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-4-pyridin-3-yl-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-4-pyridin-3-yl-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D. Off-white solid. MS 393.2 ($[M+H]^+$)

Example 74

74.1

In analogy to example 57.1 (RS)-N-(4-cyano-benzyl)-2-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2-methoxy-acetamide (example 73.1) was reacted with 4-bromopyridine, hydrochloride to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-pyridin-4-yl-phenyl)-2-methoxy-acetamide. Light brown amorphous solid. MS 376.3 ($[M+H]^+$)

74.2

(RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-pyridin-4-yl-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-4-pyridin-4-yl-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D. Off-white solid. MS 393.2 ($[M+H]^+$)

Example 75

75.1

5-Bromo-2-fluorobenzaldehyde was converted to (RS)-(5-bromo-2-fluoro-phenyl)-methoxy-acetic acid according to general procedure A using methanol/dioxane as solvent. Light yellow liquid. MS 262.0 ($[M-H]^-$)

75.2

(RS)-(5-Bromo-2-fluoro-phenyl)-methoxy-acetic acid was reacted with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-2-(5-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Colorless solid. MS 377.2 ($[M+H]^+$)

75.3

(RS)-2-(5-Bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to (RS)-2-(5-bromo-2-fluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-methoxy-acetamide; hydrochloride according to general procedure D. Colorless solid. MS 394.0 ($[M+H]^+$)

Example 76

76.1

In analogy to example 57.1 give (RS)-2-(5-bromo-2-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide (example 75.2) was reacted with phenylboronic acid to give (RS)-N-(4-cyano-benzyl)-2-(4-fluoro-biphenyl-3-yl)-2-methoxy-acetamide. Off-white solid. MS 374.1 (M).

76.2

(RS)-N-(4-Cyano-benzyl)-2-(4-fluoro-biphenyl-3-yl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(4-fluoro-biphenyl-3-yl)-2-methoxy-acetamide; hydrochloride according to general procedure D. Colorless solid. MS 392.2 ($[M+H]^+$)

Example 77

77.1

2-Fluoro-5-methylbenzaldehyde was converted to (RS)-(2-fluoro-5-methyl-phenyl)-methoxy-acetic acid according to general procedure A using methanol/dioxane as solvent. Off-white liquid. MS 197.1 ($[M-H]^-$)

77.2

(RS)-(2-Fluoro-5-methyl-phenyl)-methoxy-acetic acid was reacted with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(2-

fluoro-5-methyl-phenyl)-2-methoxy-acetamide. Colorless amorphous solid. MS 313.2 ($[M+H]^+$)

77.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-5-methyl-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-5-methyl-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D. Colorless solid. MS 330.2 ($[M+H]^+$)

Example 78

78.1

5-(Trifluoromethyl)-2-fluorobenzaldehyde was converted to (RS)-(2-fluoro-5-trifluoromethyl-phenyl)-methoxy-acetic acid according to general procedure A using methanol/dioxane as solvent. Colorless amourphous solid. MS 251.1 ($[M-H]^-$)

78.2

(RS)-(2-Fluoro-5-trifluoromethyl-phenyl)-methoxy-acetic acid was reacted with 4-aminomethyl benzonitrile according to general procedure C to (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-5-trifluoromethyl-phenyl)-2-methoxy-acetamide. Colorless amorphous solid. MS 367.1 ($[M+H]^+$)

78.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-5-trifluoromethyl-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-5-trifluoromethyl-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D.

Example 79

79.1

2-Fluoro-6-methoxybenzaldehyde was converted to (RS)-(2-fluoro-6-methoxy-phenyl)-methoxy-acetic acid according to general procedure A using methanol/dioxane as solvent. Off-white liquid. MS 213.1 ($[M-H]^-$)

79.2

(RS)-(2-Fluoro-6-methoxy-phenyl)-methoxy-acetic acid was reacted with 4-aminomethyl benzonitrile according to general procedure C to (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-6-methoxy-phenyl)-2-methoxy-acetamide. Colorless solid. MS 329.2 ($[M+H]^+$)

79.3

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-6-methoxy-phenyl)-2-methoxy-acetamide was

converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-6-methoxy-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D.

Example 80

80.1

A solution of O-benzyl-3-fluorobenzene (4.66 g) in THF (50 ml) was cooled to –65°C. n-Buthyllithium in hexane (1.5 M, 15.8 ml) was added within 15 minutes. The reaction mixture was stirred at –65°C for 30 minutes. Then DMF (1.95 ml) was added dropwise. The reaction mixture was warmed to r.t. overnight, then poured onto ice and extracted with ethyl acetate. The organic layers were washed with brine, dried over MgSO4 and concentrated to give (RS)-2-benzyloxy-6-fluoro-benzaldehyde (4.66 g). Yellow liquid. MS 230.1 ([M]).

80.2

(RS)-2-Benzyloxy-6-fluoro-benzaldehyde was converted to (RS)-(2-benzyloxy-6-fluoro-phenyl)-methoxy-acetic acid according to general procedure A using methanol/dioxane as solvent. Yellow liquid. MS 289.1 ($[M-H]^-$)

80.3

In analogy to example 16.2 (RS)-(2-benzyloxy-6-fluoro-phenyl)-methoxy-acetic acid was converted to (RS)-(2-fluoro-6-hydroxy-phenyl)-methoxy-acetic acid. Colorless amorphous solid. MS 199.1 ($[M-H]^-$)

80.4

(RS)-(2-Fluoro-6-hydroxy-phenyl)-methoxy-acetic acid was reacted with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-6-hydroxy-phenyl)-2-methoxy-acetamide. Colorless solid. MS 315.1 ($[M+H]^+$)

80.5

(RS)-N-(4-Cyano-benzyl)-2-(2-fluoro-6-hydroxy-phenyl)-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-(2-fluoro-6-hydroxy-phenyl)-2-methoxy-acetamide; hydrochloride according to general procedure D.

Example 81

81.1

α-Bromophenylacetic acid was reacted with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-2-bromo-N-(4-cyano-benzyl)-2-phenyl-acetamide. White solid. MS 329.1 ($[M+H]^+$)

81.2

To a stirred solution of (RS)-2-bromo-N-(4-cyano-benzyl)-2-phenyl-acetamide (200 mg) in THF (10 ml) at r.t. under an Ar atmosphere were added dimethylamine, hydrochloride (149 mg), triethylamine (0.42 ml) and tetrabutylammonium iodide (34 mg). The reaction mixture was stirred for 19 hrs, then treated with additional dimethylamine, hydrochloride (149 mg) and triethylamine (0.42 ml). After another 8 hrs stirring at r.t., the solids were filtered off and washed with EtOAc. The filtrate was washed with water and brine, dried over MgSO4 and concentrated. The product was isolated by chromatography (silica gel, gradient dichloromethane => dichloromethane/MeOH 9:1) to give (RS)-N-(4-cyano-benzyl)-2-dimethylamino-2-phenyl-acetamide (165 mg). Orange solid. MS 294.3 ($[M+H]^+$)

81.3

(RS)-N-(4-Cyano-benzyl)-2-dimethylamino-2-phenyl-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-dimethylamino-2-phenyl-acetamide; hydrochloride according to general procedure D. Off-white solid. MS 311.2 ($[M+H]^+$)

Example 82

82.1

In analogy to example 81.2 of (RS)-2-bromo-N-(4-cyano-benzyl)-2-phenyl-acetamide (example 81.1) was reacted with methylamine, hydrochloride to (RS)-N-(4-cyano-benzyl)-2-methylamino-2-phenyl-acetamide. Off-white amorphous solid. MS 280.1 ($[M+H]^+$)

82.2

(RS)-N-(4-Cyano-benzyl)-2-methylamino-2-phenyl-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methylamino-2-phenyl-acetamide; hydrochloride according to general procedure D. Off-white solid. MS 297.3 ($[M+H]^+$)

Example 83

83.1

To a stirred solution of sodium methanethiolate (0.43 g) at r.t. in methanol (15 ml) were added the (RS)-2-bromo-N-(4-cyano-benzyl)-2-phenyl-acetamide (0.5 g, example 81.1) and a catalytic amount of tetrabutyl ammonium iodide. The mixture was then stirred at r.t. for 1 hr. The mixture was concentrated. The residue was taken up in EtOAc, washed with 1.0 N and brine, dried over MgSO4, filtered and concentrated. The product was isolated by chromatography (silica gel, cyclohexane/EtOAc 2:1) to give (RS)-N-(4-cyano-benzyl)-2-methylsulfanyl-2-phenyl-acetamide (0.36 g). Colorless solid. MS 297.2 ($[M+H]^+$)

83.2

(RS)-N-(4-Cyano-benzyl)-2-methylsulfanyl-2-phenyl-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methylsulfanyl-2-phenyl-acetamide; hydrochloride according to general procedure D. Colorless solid. MS 314.2 ($[M+H]^+$)

Example 84

84.1

In analogy to example 83.1 (RS)-2-bromo-N-(4-cyano-benzyl)-2-phenyl-acetamide (example 81.1) was reacted with sodium ethanethiolate to give (RS)-N-(4-cyano-benzyl)-2-ethylsulfanyl-2-phenyl-acetamide. Off-white solid. MS 311.2 ($[M+H]^+$)

84.2

(RS)-N-(4-Cyano-benzyl)-2-ethylsulfanyl-2-phenyl-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-ethylsulfanyl-2-phenyl-acetamide; hydrochloride according to general procedure D. Colorless solid. MS 328.2 ($[M+H]^+$)

Example 85

85.1

A solution of (RS)-N-(4-cyano-benzyl)-2-methylsulfanyl-2-phenyl-acetamide (0.11 g, example 83.1) in dichloromethane (10 ml) was cooled to –10°C and treated with mCPBA (0.27 g). The reaction mixture was stirred at 0°C, then diluted with dichloromethane and washed with aqueous sodium hydrogen sulfite solution. The organic layer was further washed with saturated KHCO3 solution and brine, dried over MgSO4, filtered and concentrated. The product was isolated by chromatography (silica gel, gradient cyclohexane => EtOAc) to give (RS)-N-(4-cyano-benzyl)-2-methanesulfonyl-2-phenyl-acetamide (0.084 g). White solid. MS 329.2 ($[M+H]^+$)

85.2

(RS)-N-(4-Cyano-benzyl)-2-methanesulfonyl-2-phenyl-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methanesulfonyl-2-phenyl-acetamide; hydrochloride according to general procedure D. Colorless solid. MS 346.1 ($[M+H]^+$)

Example 86

86.1

Boc-DL-phenylglycine was reacted with 4-aminomethyl benzonitrile according to general procedure C to give (RS)-[(4-cyano-benzylcarbamoyl)-phenyl-methyl]-carbamic acid tert-butyl ester. Off-white solid. MS 366.2 ($[M+H]^+$)

86.2

(RS)-[(4-Cyano-benzylcarbamoyl)-phenyl-methyl]-carbamic acid tert-butyl ester was converted to (RS)-2-amino-N-(4-carbamimidoyl-benzyl)-2-phenyl-acetamide; hydrochloride according to general procedure C. Off-white solid. MS 283.2 ($[M+H]^+$)

Example 87

87.1

A solution of give (RS)-[(4-cyano-benzylcarbamoyl)-phenyl-methyl]-carbamic acid tert-butyl ester (0.77 g, example 86.1) in dichloromethane (20 ml) was cooled to 0°C and treated with trifluoro acetic acid (5 ml). The reaction mixture was stirred at r.t. for 5 hrs, then diluted with dichloromethane, cooled to 0°C and brought to pH 9 by dropwise addition of saturated aqueous Na2CO3. The organic layer was washed with brine, dried over MgSO4, filtered and concentrated to give (RS)-2-amino-N-(4-cyano-benzyl)-2-phenyl-acetamide (0.56 g). Off-white amorphous solid. MS 266.2 ($[M+H]^+$)

87.2

A solution of (RS)-2-amino-N-(4-cyano-benzyl)-2-phenyl-acetamide (0.1 g) in dichloromethane (5 ml) was cooled to 0°C and treated with triethylamine (58 µl) and acetyl chloride (28 µl). The reaction mixture was stirred at r.t. for 1 hr, then diluted with dichloromethane, washed with 1N HCl and brine. The organic layer was dried over MgSO4, filtered and concentrated. The product was isolated by chromatography (silica gel, gradient dichloromethane => dichloromethane/MeOH 9:1) to give (RS)-2-acetylamino-N-(4-cyano-benzyl)-2-phenyl-acetamide (98 mg). Off-white solid. MS 308.2 ($[M+H]^+$)

87.3

(RS)-2-Acetylamino-N-(4-cyano-benzyl)-2-phenyl-acetamide was converted to (RS)-2-acetylamino-N-(4-carbamimidoyl-benzyl)-2-phenyl-acetamide; hydrochloride according to general procedure D.

Example 88

88.1

In analogy to example 22.1, (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-4-hydroxy-phenyl)-2-methoxy-acetamide (example 70.4) was reacted with 2-phenoxyethanol, diethyl azodicarboxylate and triphenyl-phosphine in THF to give (RS)-N-(4-cyano-benzyl)-2-[2-fluoro-4-(2-phenoxy-ethoxy)-phenyl]-2-methoxy-acetamide. Colorless oil. MS 435.3 ($[M+H]^+$)

88.2

(RS)-N-(4-Cyano-benzyl)-2-[2-fluoro-4-(2-phenoxy-ethoxy)-phenyl]-2-methoxy-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-[2-fluoro-4-(2-phenoxy-ethoxy)-phenyl]-2-methoxy-acetamide hydrochloride according to general procedure D. White solid. MS 452.2 ($[M+H]^+$)

Example 89

89.1

2-Pyridinecarboxaldehyde was converted to (RS)-methoxy-pyridin-2-yl-acetic acid according to general procedure A using methanol/dioxane as solvent. Brown oil. MS 166.1 ($[M-H]^-$)

89.2

(RS)-Methoxy-pyridin-2-yl-acetic acid was reacted with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-pyridin-2-yl-acetamide. Brown oil. MS 282.2 ($[M+H]^+$)

89.3

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-pyridin-2-yl-acetamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-pyridin-2-yl-acetamide hydrochloride according to general procedure D. Off-white, amorphous solid. MS 299.2 ($[M+H]^+$)

Example 90

90.1

Acetophenone was converted to (RS)-2-methoxy-2-phenyl-propionic acid according to general procedure A using methanol/dioxane as solvent. Brown oil. MS 179.1 ($[M-H]^-$)

90.2

(RS)-2-Methoxy-2-phenyl-propionic acid was reacted with 4-aminomethyl benzonitrile according to general procedure B to give (RS)-N-(4-cyano-benzyl)-2-methoxy-2-phenyl-propionamide. Off-white, waxy solid. MS 295.0 ($[M+H]^+$)

90.3

(RS)-N-(4-Cyano-benzyl)-2-methoxy-2-phenyl-propionamide was converted to (RS)-N-(4-carbamimidoyl-benzyl)-2-methoxy-2-phenyl-propionamide hydrochloride according to general procedure D. Off-white, amorphous solid. MS 312.2 ($[M+H]^+$)

Example 91

91.1

The crude 4-bromo-2,6-difluorobenzaldehyde described in example 69.1 was reacted according to general procedure A using ethanol / dioxane as a solvent. The product of this reaction was subsequently coupled with 4-aminomethyl benzonitrile according to general procedure B. The product of this reaction could not be obtained pure and was directly converted to (RS)-2-(4-bromo-2,6-difluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-acetamide hydrochloride according to general procedure D. Off-white solid. MS 426.2($[M+H]^+$)

Example 92

92.1

In analogy to example 16.4 (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-6-hydroxy-phenyl)-2-methoxy-acetamide (example 80.4) was reacted with 2-bromoethanol in the presence of cesium carbonat in DMF to give N-(4-cyano-benzyl)-2-[2-fluoro-6-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide. White solid. MS 359.2($[M+H]^+$)

92.1

N-(4-Cyano-benzyl)-2-[2-fluoro-6-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide was converted to N-(4-carbamimidoyl-benzyl)-2-[2-fluoro-6-(2-hydroxy-ethoxy)-phenyl]-2-methoxy-acetamide; hydrochloride according to general procedure D. White solid. MS 376.3 ($[M+H]^+$)

Example 93

93.1

In analogy to example 16.4 (RS)-N-(4-cyano-benzyl)-2-(2-fluoro-6-hydroxy-phenyl)-2-methoxy-acetamide (example 80.4) was reacted with iodo acetamide in the presence of potassium carbonate in DMF to give 2-(2-carbamoylmethoxy-6-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide. Solid. MS 372.2 ($[M+H]^+$)

93.2

2-(2-Carbamoylmethoxy-6-fluoro-phenyl)-N-(4-cyano-benzyl)-2-methoxy-acetamide was converted to N-(4-carbamimidoyl-benzyl)-2-(2-carbamoylmethoxy-6-fluoro-phenyl)-2-methoxy-acetamide; hydrochlorideaccording to general procedure D. White solid. MS 389.2 ($[M+H]^+$)

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcristalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidon in water. The granulate is mixed with sodium starch glycolate and magesiumstearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents

Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

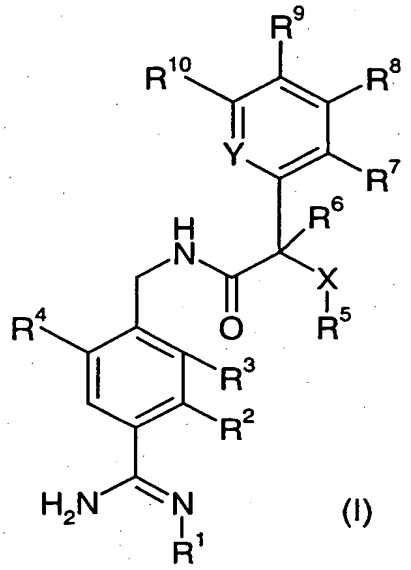
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcristalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcristalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesiumstearate and the flavouring additives and filled into sachets.

Claims:

1. Compounds of the formula (I)



(I)

wherein

R^1 is hydrogen, OH, NH_2, lower-alkoxy-carbonyl, aryl-lower-alkoxy-carbonyl, aryloxy-carbonyl, lower-alkyl-carbonyl, aryl-carbonyl, or lower-alkoxy-carbonyl which is substituted with halogen;

R^2, R^3 and R^4 independently from each other are selected from the group consisting of hydrogen, halogen, hydroxy, and lower-alkoxy, which lower-alkoxy can optionally be substituted with hydroxy, carboxy or carbamoyl;

R^5 is lower-alkyl or cycloalkyl, or, if X is O or NR^{12}, R^5 can also be hydrogen;

R^6 is hydrogen, lower-alkyl, or fluoro-lower-alkyl;

Y is N or C-R^{11};

R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, hydroxy, halogen, amino, lower-alkyl-amino, di-lower-alkyl-amino, lower-alkyl-carbonyl-amino, NO_2, fluoro-lower-alkyl, lower-alkoxy, hydroxy-lower-alkoxy, fluoro-lower-alkoxy, lower-alkinyl, hydroxy-lower-alkinyl, aryl, aryl-lower-alkoxy, aryloxy, aryloxy-lower-alkoxy, heterocyclyl, heterocyclyloxy, lower-alkoxy-carbonyl-lower-alkoxy, carbamoyl-lower-alkoxy, carboxy-lower-alkoxy, cycloalkyloxy, heteroaryl, amino-lower-

alkoxy, lower-alkyl-amino-lower-alkoxy, and di-lower-alkyl-amino-lower-alkoxy,

or

R^8 and R^9 or R^8 and R^7 are bound to each other to form a ring together with the carbon atoms to which they are attached and R^8 and R^9 together or R^8 and R^7 together are -O-CH_2-O-, -O-CH_2-CO-NH-, -O-CH_2-CH_2-CH_2-, or -CH=CH-CH=CH-, which can optionally be substituted with lower-alkyl or lower-alkoxy, and R^{10}, R^{11} and R^7 or R^9 respectively are as definde above;

X is O, S, NR^{12}, or SO_2;

R^{12} is hydrogen, lower-alkyl, or lower-alkyl-carbonyl;

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein R^1 is hydrogen, OH, NH_2, or lower-alkoxy-carbonyl.

3. Compounds according to any of claims 1 - 2, wherein R^1 is hydrogen, OH, or lower-alkoxy-carbonyl.

4. Compounds according to any of claims 1 – 3, wherein R^1 is hydrogen, OH, or ethoxycarbonyl.

5. Compounds according to any of claims 1 – 4, wherein R^1 is hydrogen.

6. Compounds according to any of claims 1 – 5, wherein R^2, R^3 and R^4 independently from each other are hydrogen or halogen.

7. Compounds according to any of claims 1 – 6, wherein R^2, R^3 and R^4 are hydrogen.

8. Compounds according to any of claims 1 – 7, wherein X is O.

9. Compounds according to any of claims 1 – 8, wherein R^5 is lower-alkyl.

10. Compounds according to any of claims 1 – 9, wherein R^5 is methyl or ethyl.

11. Compounds according to any of claims 1 – 10, wherein R^6 is hydrogen, methyl, or CF_3.

12. Compounds according to any of claims 1 – 11, wherein R^6 is hydrogen.

13. Compounds according to any of claims 1 – 12, wherein Y is C-R^{11} and R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, hydroxy, halogen, di-lower-alkyl-amino, lower-alkyl-carbonyl-amino, NO_2, fluoro-lower-alkyl, lower-alkoxy, hydroxy-lower-alkoxy, fluoro-lower-alkoxy, aryl, aryl-lower-alkoxy, aryloxy, aryloxy-lower-alkoxy, heterocyclyl, heterocyclyloxy, lower-alkoxy-carbonyl-lower-alkoxy, carbamoyl-lower-alkoxy, carboxy-lower-alkoxy, cycloalkyloxy, heteroaryl, and di-lower-alkyl-amino-lower-alkoxy.

14. Compounds according to any of claims 1 – 13, wherein Y is C-R^{11} and R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, halogen, lower-alkoxy, and pyridyl.

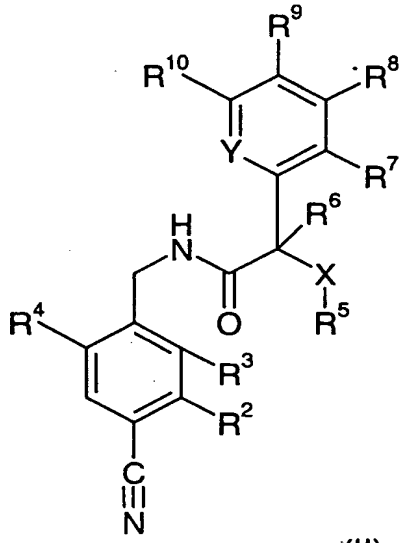
15. Compounds according to any of claims 1 – 14, wherein Y is C-R^{11} and R^7, R^8, R^9, R^{10} and R^{11} independently from each other are selected from the group consisting of hydrogen, fluoro, bromo, methoxy, and pyridyl.

16. Compounds according to any of claims 1 – 12, wherein Y is C-R^{11}, R^8 and R^9 or R^8 and R^7 are bound to each other to form a ring together with the carbon atoms to which they are attached and R^8 and R^9 together or R^8 and R^7 together are -O-CH_2-O-, -O-CH_2-CO-NH-, -O-CH_2-CH_2-CH_2-, or -CH=CH-CH=CH-, which can optionally be substituted with lower-alkyl or lower-alkoxy, and R^{10}, R^{11} and R^7 or R^9 respectively are hydrogen.

17. Compounds according to any of claims 1 - 16, selected from the group consisting of
(S)-N-(4-Carbamimidoyl-benzyl)-2-methoxy-2-phenyl-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,
(RS)-[Amino-(4-{[2-(2-fluoro-4-methoxy-phenyl)-2-methoxy-acetylamino]-methyl}-phenyl)-methylene]-carbamic acid ethyl ester,
(RS)-2-(2-Fluoro-4-methoxy-phenyl)-N-[4-(N-hydroxycarbamimidoyl)-benzyl]-2-methoxy-acetamide,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(3-fluoro-3'-methoxy-biphenyl-4-yl)-2-methoxy-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-ethoxy-2-(2-fluoro-4-methoxy-phenyl)-acetamide hydrochloride,
(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2,6-difluoro-4-methoxy-phenyl)-2-methoxy-acetamide hydrochloride,

(RS)-N-(4-Carbamimidoyl-benzyl)-2-(2-fluoro-4-pyridin-3-yl-phenyl)-2-methoxy-acetamide hydrochloride, and
(RS)-2-(4-Bromo-2,6-difluoro-phenyl)-N-(4-carbamimidoyl-benzyl)-2-ethoxy-acetamide hydrochloride,
and pharmaceutically acceptable salts thereof.

18. A process for the manufacture of compounds of formula (I) as defined in any of claims 1 – 17, which process comprises converting the nitrile group in a compound of formula (II)

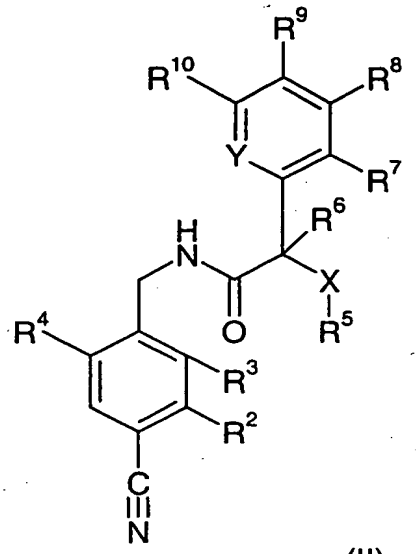


(II)

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X and Y have the significances given in any of claims 1 - 16, into a carbamimidoyl group, or into a N-hydroxy-carbamimidoyl group, or into a N-amino-carbamimidoyl group, and, if desired, converting an obtained compound of formula (I) into a pharmaceutically acceptable salt.

19. Compounds according to any of claims 1 - 17, when manufactured by a process according to claim 18.

20. Compounds of formula (II)



(II)

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X and Y have the significances given in any of claims 1 - 16.

21. Pharmaceutical compositions comprising a compound according to any of claims 1 - 17 and a pharmaceutically acceptable carrier and/or adjuvant.

22. Compounds according to any of claims 1 - 17 for use as therapeutic active substances.

23. Compounds according to any of claims 1 - 17 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with the formation of clotting factors Xa, IXa and thrombin induced by factor VIIa and tissue factor.

24. A method for the therapeutic and/or prophylactic treatment of diseases which are asscociated with the formation of clotting factors Xa, IXa and thrombin induced by factor VIIa and tissue factor, particularly for the therapeutic and/or prophylactic treatment of arterial and venous thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation, arteriosclerosis and/or tumour, which method comprises administering a compound according to any of claims 1 - 17 to a human being or animal.

25. The use of compounds according to any of claims 1 - 17 for the therapeutic and/or prophylactic treatment of diseases which are asscociated with the formation of clotting factors Xa, IXa and thrombin induced by factor VIIa and tissue factor.

26. The use of compounds according to any of claims 1 - 17 for the therapeutic and/or prophylactic treatment of arterial and venous thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation, arteriosclerosis and/or tumour.

27. The use of compounds according to any of claims 1 - 17 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are asscociated with the formation of clotting factors Xa, IXa and thrombin induced by factor VIIa and tissue factor.

28. The use of compounds according to any of claims 1 - 17 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of arterial and venous thrombosis, deep vein thrombosis, pulmonary embolism, unstable angina pectoris, cardiac infarction, stroke due to atrial fibrillation, inflammation, arteriosclerosis and/or tumour.

29. The invention as hereinbefore defined.

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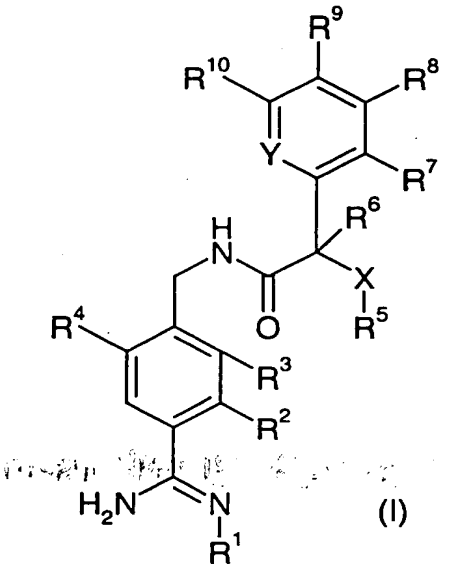
Abstract

The invention is concerned with novel mandelic acid derivatives of formula (I)



(I)

wherein R^1 to R^{10}, X and Y are as defined in the description and in the claims, as well as physiologically acceptable salts thereof. These compounds inhibit the formation of coagulation factors Xa, IXa and thrombin induced by factor VIIa and tissue factor and can be used as medicaments